

Sterne Kessler  
Goldstein Fox

March 5, 2003

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Commissioner for Patents  
Washington, D.C. 20231

***Hand Carry to Examiner W. Moore***  
***Art Unit 1652***

Re: U.S. Utility Patent Application  
Appl. No. 10/024,131; Filed: December 21, 2001  
For: **Cloned Genes Encoding Reverse Transcriptase  
Lacking RNase H Activity**  
Inventors: KOTEWICZ *et al.*  
Our Ref: 0942.049000B/RWE/MTT

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement and list of cited references on Form PTO-1449 (13 sheets);
2. First Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (3 sheets);
3. Second Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (11 sheets);
4. Third Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (3 sheets);
5. Fourth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (26 sheets);
6. Fifth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (1 sheet);

Commissioner for Patents  
March 5, 2003  
Page 2

7. Sixth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**15** sheets);
8. Seventh Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**3** sheets);
9. Eighth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**32** sheets);
10. Ninth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**8** sheets);
11. Tenth Supplemental Information Disclosure Statement;
12. Eleventh Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**2** sheets);
13. Twelfth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**1** sheet);
14. Thirteenth Supplemental Information Disclosure Statement and list of cited references on Form PTO-1449 (**5** sheets);
15. Fourteenth Supplemental Information Disclosure Statement, list of cited references on Form PTO-1449 (**5** sheets), and a copy of each reference cited on Form PTO-1449 (**21** documents: **AH1-AB2, AM1, and AS112-AT116**); and
16. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents

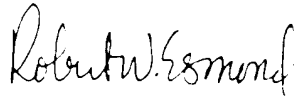
March 5, 2003

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The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

RWE/MTT/acr  
Enclosures

SKGF\_DC1:99390.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10 024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Information Disclosure Statement**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. All documents were cited by or submitted to the Office in Application No. 08/798,458, filed February 10, 1997, which issued as U.S. Patent No. 6,063,608; Application No. 08/614,260, filed March 12, 1996, which issued as U.S. Patent No. 5,668,005, on September 16, 1997; Application No. 08/404,907, filed March 15, 1995; Application No. 07/671,156, filed March 18, 1991, which issued as U.S. Patent No. 5,244,797 on September 14, 1993, and was reexamined as Control No. 90/003,803; and Application No. 07/825,260, filed January 24, 1992, which issued as U.S. Patent No. 5,405,776 on April 11, 1995 and was reexamined as Control No. 90/003,804. Copies of the cited documents may be found in these parent applications and are not enclosed.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior



art, and or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

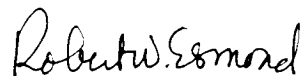
This Information Disclosure Statement is being filed more than three months after the U.S. filing date but before the mailing date of a first Office Action on the merits. No statement or fee is required.

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA1	4,663,290	05/05/1987	Weis et al.	435	253	01/21/1982
	AB1	4,795,699	01/03/1989	Tabor et al.	435	5	01/14/1987
	AC1	4,943,531	07/24/1990	Goff et al.	435	194	05/06/1985
	AD1	5,017,492	05/21/1991	Kotewicz et al.	435	252.3	02/27/1986
	AE1	5,244,797	09/14/1993	Kotewicz et al.	435	194	03/18/1991
	AF1	5,405,776	04/11/1995	Kotewicz et al.	435	252.33	01/24/1992
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	1	Akins, R.A. et al., "Mitochondrial Plasmids of Neurospora: Integration into Mitochondrial DNA and Evidence for Reverse Transcription in Mitochondria," <i>Cell</i> 47:505-516, Cell Press (1986).
AS	1	Bassin, R.H. et al., "Macromolecular Requirements for Abrogation of Fv-1 Restriction by Murine Leukemia Viruses," <i>J. Virology</i> 35(2):287-297, American Society for Microbiology (1980).
AT	1	Berger, S.L. et al., "Reverse Transcriptase and Its Associated Ribonuclease H: Interplay of Two Enzyme Activities Controls the Yield of Single-Stranded Complementary Deoxyribonucleic Acid," <i>Biochemistry</i> 23:2365-2372, American Chemical Society (1983).

EXAMINER

DATE CONSIDERED

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	AN						Yes No
	AO						Yes No
	AP						Yes No

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

	AR	<u>2</u>	Blain, S.W. and Goff, S.P., "Nuclease Activities of Moloney Murine Leukemia Virus Reverse Transcriptase," <i>J. Biol. Chem.</i> 268(31):23585-23592, American Society for Biochemistry and Molecular Biology, Inc. (1993).
	AS	<u>2</u>	Carter, P. and Wells, J.A., "Engineering Enzyme Specificity by 'Substrate-Assisted Catalysis,'" <i>Science</i> 237 394-399, American Association for the Advancement of Science (1987).
	AT	<u>2</u>	Fawcett, D.H. et al., "Transposable Elements Controlling I-R Hybrid Dysgenesis in <i>D. melanogaster</i> Are Similar to Mammalian LINES," <i>Cell</i> 47:1007-1015, Cell Press (1986).

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	AM						Yes No
	AN						Yes No
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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>3</u>	Finston, W.I. and Champoux, J.J., "RNA-Primed Initiation of Moloney Murine Leukemia Virus Plus Strands by Reverse Transcriptase In Vitro," <i>J. Virology</i> 51(1):26-33, American Society for Microbiology (1984).	
AS	<u>3</u>	Gerard, G.F. et al., "Poly (2'-O-methylcytidylate) Oligodeoxyguanylate as a Template for the Ribonucleic Acid Directed Deoxyribonucleic Acid Polymerase in Ribonucleic Acid Tumor Virus Particles and a Specific Probe for the Ribonucleic Acid Directed Enzyme in Transformed Murine Cells," <i>Biochemistry</i> 13(8):1632-1641, Academic Press, Inc. (1974).	
AT	<u>3</u>	Gerard, G.F. and Grandgenett, D.P., "Purification and Characterization of the DNA Polymerase and RNase H Activities in Moloney Murine Sarcoma-Leukemia Virus," <i>J. Virology</i> 15(4):785-797, American Society for Microbiology (1975).	

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**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

	AR	<u>4</u>	Gerard, G.F., "Multiple RNase H Activities in Mammalian Type C Retrovirus Lysates," <i>J. Virology</i> 26(1):16-28, American Society for Microbiology (1978).
	AS	<u>4</u>	Gerard, G.F., "Mechanism of Action of Moloney Murine Leukemia Virus RNase H III," <i>J. Virology</i> 37(2):748-754, American Society for Microbiology (1981).
	AT	<u>4</u>	Gerard, G.F. et al., "Influence on Stability in <i>Escherichia coli</i> of the Carboxy-Terminal Structure of Cloned Moloney Murine Leukemia Virus Reverse Transcriptase," <i>DNA</i> 5(4):271-279, Mary Ann Liebert, Inc. (1986).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>5</u>	Gerwin, B.I. et al., "Mutant of B-Tropic Murine Leukemia Virus Synthesizing an Altered Polymerase Molecule," <i>J. Virology</i> 31(3):741-751, American Society for Microbiology (1979).
AS	<u>5</u>	Gorecki, M. and Panet, A., "Discrimination of DNA Polymerase and RNase H Activities in Reverse Transcriptase of Avian Myeloblastosis Virus," <i>Biochemistry</i> 17(12):2438-2442, American Chemical Society (1978).
AT	<u>5</u>	Johnson, M.S. et al., "Computer analysis of retroviral pol genes: Assignment of enzymatic functions to specific sequences and homologies with nonviral enzymes," <i>Proc. Natl. Acad. Sci. USA</i> 83:20:7648-7652, National Academy of Sciences (1986).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	6	Kamer, G. and Argos, P., "Primary structural comparison of RNA-dependent polymerases from plant, animal and bacterial viruses," Nucl. Acids. Res. 12(18):7269-7282, IRL Press Ltd. (1984).
AS	6	Kotewicz, M.L. et al., "Cloning and overexpression of Moloney murine leukemia virus reverse transcriptase in <i>Escherichia coli</i> ," Gene 35:249-258, Elsevier Science Publishers (1985).
AT	6	Kotewicz, M.L. et al., "Isolation of cloned Moloney murine leukemia virus reverse transcriptase lacking ribonuclease H activity," Nucl. Acids Res. 16(1):265-277, IRL Press Ltd. (1988).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	7	Lai, M.-H.T. and Verma, I.M., "Reverse Transcriptase of RNA Tumor Viruses. V. In Vitro Proteolysis of Reverse Transcriptase from Avian Myeloblastosis Virus and Isolation of a Polypeptide Manifesting Only RNase H Activity," J. Virology 25(2):652-663, American Society for Microbiology (1978).	
AS	7	Lai, M.-H.T. et al., "Mammalian Retrovirus-Associated RNase H Is Virus Coded," J. Virology 27(3):823-825, American Society for Microbiology (1978).	
AT	7	Levin, J.G. et al., "Murine Leukemia Virus Mutant with a Frameshift in the Reverse Transcriptase Coding Region: Implications for pol Gene Structure," J. Virology 51(2):470-478, American Society for Microbiology (1984).	

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	8	Maniatis, T. In: <i>Molecular Cloning, A Laboratory Manual</i> , Maniatis, T et al., eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 213 and 231 (1982).
	AS	8	Meloun, B. et al., "Complete primary structure of thermitase from <i>Thermoactinomyces vulgaris</i> and its structural features related to the subtilisin-type proteinases," <i>FEBS Letters</i> 183(2):195-200, North-Holland Press (1985).
	AT	8	Messer, L.I. et al., "Functional Analysis of Reverse Transcription by a Frameshift pol Mutant of Murine Leukemia Virus," <i>Virology</i> 146:146-152, Academic Press, Inc. (1985).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	2	Michel, F. and Lang, B.F., "Mitochondrial class II introns encode proteins related to the reverse transcriptases of retroviruses," Nature 316:641-643, Macmillan Journals Ltd. (1985).	
AS	2	Moelling, K. and Friis, R.R., "Two Avian Sarcoma Virus Mutants with Defects in the DNA Polymerase-RNase H Complex," J. Virology 32(2):370-378, American Society for Microbiology (1979).	
AT	2	Resnick, R. et al., "Involvement of Retrovirus Reverse Transcriptase-Associated RNase H in the Initiation of Strong-Stop (+) DNA Synthesis and the Generation of the Long Terminal Repeat," J. Virology 51(3):813-821, American Society for Microbiology (1984).	

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>10</u>	Roth, M.J. et al., "Purification and Characterization of Murine Retroviral Reverse Transcriptase Expressed in <i>Escherichia coli</i> ," <i>J. Biol. Chem.</i> 260(16):9326-9335, American Society of Biological Chemists, Inc. (1985).	
AS	<u>10</u>	Shinnick, T.M. et al., "Nucleotide sequence of Moloney murine leukaemia virus," <i>Nature</i> 293:543-548, Macmillan Journals Ltd. (1981).	
AT	<u>10</u>	Smith, J.K. et al., "Initiation of Plus-Strand DNA Synthesis During Reverse Transcription of an Avian Retrovirus Genome," <i>J. Virology</i> 49(1):200-204, American Society for Microbiology (1984).	

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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>11</u>	Tanese, N. et al., "Analysis of Retroviral pol Gene Products with Antisera Raised against Fusion Proteins Produced in <i>Escherichia coli</i> ," <i>J. Virology</i> 59(2):328-340, American Society for Microbiology (1986).	
AS	<u>11</u>	Tanese, N. et al., "Expression of enzymatically active reverse transcriptase in <i>Escherichia coli</i> ," <i>Proc. Natl. Acad. Sci. USA</i> 82(15):4944-4948, National Academy of Sciences (1985).	
AT	<u>11</u>	Telesnitsky, A. and Goff, S.P., "RNase H domain mutations affect the interaction between Moloney murine leukemia virus reverse transcriptase and its primer-template," <i>Proc. Natl. Acad. Sci. USA</i> 90:1276-1280, National Academy of Sciences 1993.	

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>12</u>	Toh, H. et al., "Sequence homology between retroviral reverse transcriptase and putative polymerases of hepatitis B virus and cauliflower mosaic virus," <i>Nature</i> 305:827-829, Macmillan Journals Ltd. (1983).
	AS	<u>12</u>	Tronick, S.R. et al., "Molecular cloning of Moloney murine sarcoma virus: Arrangement of virus-related sequences within the normal mouse genome," <i>Proc. Natl. Acad. Sci. USA</i> 76(12):6314-6318, National Academy of Sciences (1979).
	AT	<u>12</u>	Van Beveren, C. et al., "RNA Tumor Viruses" in <i>Molecular Biology of Tumor Viruses</i> , 2nd ed., vol. 2. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 773-779 (1985).

EXAMINER	DATE CONSIDERED
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	13	Zoller, M.J. and Smith, M., "Oligonucleotide-Directed Mutagenesis of DNA Fragments Cloned into M13 Vectors," <i>Methods in Enzymology</i> 100:468-500, Academic Press, Inc. (1983).	
AS			
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**First Supplemental Information Disclosure Statement**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this First Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by or submitted to the Office in Application No. 08/798,458, filed February 10, 1997.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

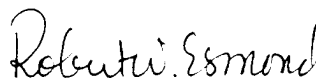
This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This First Supplemental Information Disclosure Statement is being filed more than three months after the U.S. filing date but before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

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FORM PTO-1449 FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AE		
	AS	13	Brewer, L.C. and Wells, R.D., "Mechanistic Independence of Avian Myeloblastosis Virus DNA Polymerase and Ribonuclease H," J. Virol. 14:1494-1502, American Society for Microbiology (1974)
	AT	13	Kimmel, A.R. and Berger, S.L., "Preparation of cDNA and the Generation of cDNA Libraries: Overview," Meth. Enzymol. 152:307-389, Academic Press, Inc. (1987)

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	14	Myers, J.C. and Spiegelman, S., "Sodium pyrophosphate inhibition of RNA•DNA hybrid degradation by reverse transcriptase," <i>PNAS USA</i> :75:5329-5333, National Academy of Sciences (1978).
	AS	14	Rho, H.M., "Biochemical and Immunological Characterization of the DNA Polymerase and RNase H in Feline Leukemia Virus," <i>Korean J. Zoology</i> 22 141-152, Seoul Tuxpyolsi: Han'guk Tongmul Hakhoe (1979)
	AT	14	Rho, H.M. and Gallo, R.C., "Biochemical and Immunological Properties of the DNA Polymerase and RNase H Activities of Purified Feline Leukemia Virus Reverse Transcriptase," <i>Cancer Letters</i> 10:207-221, Elsevier/North Holland Scientific Publisher Ltd. (1980)

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	APPLICANTS Kotewicz et al.	
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	AN						Yes No
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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>15</u>	Weiss, J. et al., "Production and Characterization of Monoclonal Antibodies Against Avian Retrovirus Reverse Transcriptase," J. Virol. 45:859-863, American Society for Microbiology (1983)
	AS	<u>15</u>	Weiss, R. et al., eds., Molecular Biology of Tumor Viruses, 2d edition, Chapter 5, "RNA Tumor Viruses," pp. 75-80, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1985).
	AT		

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10 024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Second Supplemental Information Disclosure Statement**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Second Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' First Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by or submitted to the Office in Application No. 08/798,458, filed February 10, 1997.

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art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

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Applicants also wish to bring the following information to the attention of the Examiner.

Life Technologies, Inc. (LTI) was the initial owner of related U.S. Patent Nos. 5,244,797 and 5,668,005. LTI and Invitrogen Corporation subsequently merged in September, 2000, with Invitrogen Corporation being the surviving entity. Thus, Invitrogen Corporation is now the owner of these patents as well as the present application.

On December 31, 1996, LTI filed suit against Clontech Laboratories, Inc. (Clontech) in U.S. District Court for the District of Maryland, alleging infringement of U.S. Patent No. 5,244,797. Subsequent thereto, and following issuance of the '005 patent, LTI amended its Complaint to also allege infringement of that patent.

In its defense, Defendant Clontech has raised numerous defenses, alleging, *inter alia*, that the patents are invalid and unenforceable. Cited herewith, consistent with the Federal Circuit's decision in *Critikon v. Becton Dickinson Vascular Access*, 43 USPQ2d 1666 (1997), is Defendant Clontech's Supplemental Response to Plaintiff's Interrogatory No. 13, setting forth the basis for each of Defendant Clontech's defenses, as well as certain of the documents referred to therein.

In addition, Defendant Clontech has filed motions for summary judgment alleging that the patents are (1) invalid for failure to disclose the best mode and (2) unenforceable due to inequitable conduct.

Defendant Clontech's motion for summary judgment on the issue of best mode presents the following additional alleged evidence that is not set forth with particularity in its Supplemental Response to Plaintiff's Interrogatory No. 13:

- (1) LTI's August 1987 Molecular Biology R&D Monthly Status Report states the following:

"Our best deletion mutant, pRTdR5-Bal31 #14 was transferred to E. coli N4830. Dave Clark has grown up and induced these cells. They are ready to be cracked open and the RT tested for H levels and efficiency of first strand synthesis. This mutant is our best candidate for a new RNase H minus RT to market."

- (2) William Enright, LTI's 30(b)(6) witness, testified as follows:

Q: . . . Is it correct that the enzyme which LTI was looking for would have as high a DNA polymerase activity as possible, and as low an RNase H activity as possible?

A: Yes

Q: And the 14N encoded enzyme had better characteristics in that regard than the enzymes encoded by previous plasmids?

A: Yes

- (3) In crude extract screenings performed prior to filing of patent application, 14N showed a better DNA polymerase to RNase H ratio (.01) than the clone, RV-C, disclosed in the patent (.03).

Defendant Clontech's motion for summary judgment of unenforceability presents the following additional alleged evidence that is not set forth with particularity in its Supplemental Response to Plaintiff's Interrogatory No. 13:

- (1) Mark Berninger, LTI's former in-house intellectual property manager, wrote a note to inventor Gary Gerard that reads:

The major publication threat to the RNase deficient RT patent comes from Goff, not ourselves. We should be sure to file before Goff publishes assuming we will

file (the attorneys had serious questions concerning the patentability of this invention) . . . .

- (2) In Applicant's January 30, 1990, response filed in connection with the patent application that matured into the '797 patent, Applicant asserted that "[u]ntil Applicants actually prepared a truncated reverse transcriptase enzyme, it was not known whether a molecule having DNA polymerase activity and substantially no RNase activity could actually be prepared. . . . Applicants were the first to prepare a reverse transcriptase having DNA polymerase activity and substantially no RNase H activity."
- (3) In Applicant's March 18, 1991, Request for Reconsideration, Applicant asserted that "[u]ntil Applicants actually prepared a truncated [RT], it was not known whether such an enzyme could actually be made. . . . In the intervening years between these publication dates [1978-1981] and Applicants' date of invention, no one was able to separate DNA polymerase and RNase activity."

In its motion, Clontech alleges that LTI made the foregoing statements knowing full well that Goff had succeeded in generating mutants of cloned M-MLV RT that lack RNase H activity. However, neither the Invention Disclosure Form nor the information about Goff's work was provided to the PTO. Instead, in order to gain allowance of the claims at issue, LTI intentionally suppressed Goff's work and steadfastly asserted itself to be the first and only to achieve an RT which lacked RNase H activity.

Clontech also alleged that the Applicants misled the PTO by signing the patent application oath in which they declared that they, not Goff, were the first to invent the claimed subject matter.

Finally, Defendant Clontech Laboratories, Inc. filed a motion to disqualify Applicant's litigation counsel from representing Applicant in the litigation due to an interview that the

examiner conducted with litigation counsel Peter J. Davis on September 8, 1997, just prior to the issuance of the '005 patent.<sup>1</sup> In that motion, Defendant Clontech Laboratories, Inc. asserted that

1. Mr. Davis did not have a power of attorney.
2. Disclosing information to the PTO only eight days before issuance guarantees that the information will not affect the issuance of the patent.
3. Late disclosure is suspicious since LTI had been aware of the information all along, and it was not disclosed during prosecution of '797 patent.
4. The Examiner no longer had jurisdiction over the case, and the interview was thus improper.
5. The interview was an attempt to purge inequitable conduct with respect to the '005 patent.
6. Mr. Davis did not leave the cited documents with examiner.
7. It is unlikely the examiner had possession of the file during the interview since it should have been at Issue Branch at that time.
8. LTI intentionally waited until after allowance before disclosing the Invention Disclosure Form.

Defendant Clontech also asserted in its motion to disqualify Applicant's litigation counsel that, with respect to an April 9, 1998 Information Disclosure Statement filed in the reexamination of a related patent, LTI consciously waited until the reexamination proceedings on the merits had been closed before submitting a copy of the interview summary record, since the IDS was filed after the Notice of Intent to Issue Reexamination Certificate had issued and more than 7 months after interview took place. Clontech also asserted that none of the underlying documentation was provided to the PTO. In addition, Clontech asserted that the submission of the interview

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<sup>1</sup>In parent application no. 08/798,458, copies of the documents that were discussed at the interview of September 8, 1997, with respect to the '005 patent, as well as other documentary evidence that came to light in the litigation, were submitted for consideration by the Examiner.



summary record in the reexamination proceeding was not only unusual, but demonstrates the high materiality of the information disclosed by Mr. Davis at the interview.

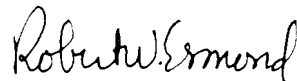
This disclosure is made in view of the Federal Circuit's decision in *Critikon*. This disclosure should not be construed as an admission that any of the information disclosed herein or herewith is material. Should the Examiner require clarification or additional information concerning any of the matters set forth herein, he is invited to contact Applicant's representative at the number indicated below.

This Second Supplemental Information Disclosure Statement is being filed more than three months after the U.S. filing date but before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449 SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR		
	AS		
	AT	15	Berger, S.L. et al., "Reverse Transcriptase and Its Associated Ribonuclease H: Interplay of Two Enzyme Activities Controls the Yield of Single-Stranded Complementary Deoxyribonucleic Acid," <i>Biochem. 22</i> :2365-2372, American Chemical Society (1983)

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FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.04900CB/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
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	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>16</u>	Dudding, L.R. et al., "Analysis of the RNA- and DNA-Dependent DNA Polymerase Activities of Point Mutants of HIV-1 Reverse Transcriptase Lacking Ribonuclease H Activity," <i>Biochem.</i> 30:10498-10506, American Chemical Society (October 1991)	
AS	<u>16</u>	Gubler, U. and Hoffman, B.J., "A simple and very efficient method for generating cDNA libraries," <i>Gene</i> 25:263-269, Elsevier North Holland Press (November 1983)	
AT	<u>16</u>	Hizi, A. et al., "Mutational Analysis of the Ribonuclease H Activity of Human Immunodeficiency Virus 1 Reverse Transcriptase," <i>Virology</i> 175:575-580, Academic Press, Inc. (April 1990)	

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>17</u>	Houts, G.E. et al., "Reverse Transcriptase from Avian Myeloblastosis Virus," <i>J. Virol.</i> 29:517-522, American Society for Microbiology (February 1979)
	AS	<u>17</u>	Kanaya, S. et al., "Identification of the Amino Acid Residues Involved in an Active Site of <i>Escherichia coli</i> Ribonuclease H by Site-directed Mutagenesis," <i>J. Biol. Chem.</i> 265:4615-4621, American Society for Biochemistry and Molecular Biology, Inc. (March 1990)
	AT	<u>17</u>	Mizrahi, V. et al., "Site-directed mutagenesis of the conserved Asp-443 and Asp-498 carboxy-terminal residues of HIV-1 reverse transcriptase," <i>Nucl. Acids Res.</i> 18:5359-5363, Oxford University Press (September 1990)

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>18</u>	Repaske, R. et al., "Inhibition of RNase H Activity and Viral Replication by Single Mutations in the 3' Region of Moloney Murine Leukemia Virus Reverse Transcriptase," <i>J. Virol.</i> 63:1460-1464, American Society for Microbiology (March 1989)
	AS	<u>18</u>	Schwartzberg, P. et al., "Construction and Analysis of Deletion Mutations in the pol Gene of Moloney Murine Leukemia Virus: A New Viral Function Required for Productive Infection," <i>Cell</i> 37:1043-1052, Massachusetts Institute of Technology (July 1984)
	AT	<u>18</u>	Tanese N. and Goff, S.P., "Fine-Structure Mutational Analysis of the Reverse Transcriptase Domain of Moloney Murine Leukemia Virus," <i>RNA Tumor Viruses</i> , Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (May 19-May 24, 1987)

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>19</u>	Telesnitsky, A. and Goff, S.P., "RNase H domain mutations affect the interaction between Moloney murine leukemia virus reverse transcriptase and its primer-template," <i>Proc. Natl. Acad. Sci. USA</i> 90:1276-1280, National Academy of Sciences (February 1993)
	AS	<u>19</u>	"Defendant's Supplemental Response to Plaintiff's Interrogatory No. 13," dated May 15, 1998 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AT	<u>19</u>	Letter dated October 9, 1987 from John E. Donelson, Exec. Editor of Nucleic Acids Research, Exhibit LTX 6402 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>20</u>	Referee's Report on Kotewicz' et al., "Isolation of cloned Moloney murine leukemia virus . . .," Exhibit LTX 6403 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AS	<u>20</u>	Referee's Report on Kotewicz' et al., "Isolation of cloned Moloney murine leukemia virus . . .," Exhibit LTX 6404 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AT	<u>20</u>	Letter dated November 17, 1987, from Gary F. Gerard, Ph.D., Director Enzymology, Nucleic Acids & Recombinant DNA, Molecular Biology R&D, of Bethesda Research Laboratories, Life Technologies, Inc., Exhibits LTX 6405 and LTX 6406 in <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000CB/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>21</u>	"Approval of Scientific Publications" form, Michael L. Kotewicz, requestor, dated July 24, 1987, with note attached, Exhibits LTX 6407 and LTX 6408 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AS	<u>21</u>	Memorandum from Dietmar Rabussay dated August 18, 1987, Exhibits LTX 6409 and LTX 6410 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AT	<u>21</u>	Defendant's "Answer" dated January 24, 1995 from <i>Life Technologies, Inc. v. Promega Corporation</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2776

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.



FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>22</u>	"Consent Judgment" dated March 31, 1995 from <i>Life Technologies, Inc. v. Promega Corporation</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2776
	AS	<u>22</u>	Defendant's "Answer and Counterclaim" dated February 6, 1995 from <i>Life Technologies, Inc. v. Stratagene, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2777
	AT	<u>22</u>	"Memorandum Opinion" dated July 27, 1995 from <i>Life Technologies, Inc. v. Stratagene, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2777

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>23</u>	"Order" dated July 27, 1995 from <i>Life Technologies, Inc. v. Stratagene, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2777	
AS	<u>23</u>	"Stratagene's Responses and Objections to Plaintiff's Second Set of Interrogatories to Defendant and Second Request for Production of Documents and Things" dated August 7, 1995, from <i>Life Technologies, Inc. v. Stratagene, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 94-2777, including (a) Weis, J. Virol. 45:859-863 (1983); (b) Rho & Gallo, <i>Cancer Letters</i> 10:207-221 (1980) and (c) Rho, <i>Korean Journal of Zoology</i> 22:141-152 (1970)	
AT	<u>23</u>	Defendant's "Amended Answer and Affirmative Defenses" dated July 11, 1997 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW-96-4080	

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>24</u>	"Life Technologies, Inc., Invention Disclosure Form" dated April 30, 1987, Exhibit Nos. LTX32497-LTX32502, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW-96-4080
	AS	<u>24</u>	Handwritten note by Brian Schmidt, employee of Life Technologies, Inc., Exhibit LTX35171 in <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Civil Action No. AW 96-4080
	AT	<u>24</u>	"Complaint" dated December 22, 1998, from <i>Clontech Laboratories, Inc. v. Life Technologies, Inc.</i> , U.S. District Court for the District of Delaware, Civil Action No. 98-750.

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	25	"Memorandum Opinion" and accompanying "Order" dated February 18, 1999, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.	
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AT			

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10 024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Third Supplemental Information Disclosure Statement**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Third Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Second Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by or submitted to the Office in Application No. 08/798,458, filed February 10, 1997.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior

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art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Third Supplemental Information Disclosure Statement is being filed more than three months after the U.S. filing date but before the mailing date of a first Office Action on the merits. No statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449  <u>THIRD SUPPLEMENTAL</u> <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA1	5,017,488	05/21/1991	McAllister et al.	435	194	10/17/1986
	AB1	5,668,005	09/16/1997	Kotewicz et al.	435	194	03/12/1996
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR		
	AS	25	Amuro, N. et al., "Replacement by site-directed mutagenesis indicates a role for histidine 170 in the glutamine amide transfer function of anthranilate synthase," <i>J. Biol. Chem.</i> 260:14844-14849, American Society of Biological Chemists, Inc. (1985)
	AT	25	Bryant, D.L. et al., "Amino acid alterations within a highly conserved region of the Rous sarcoma virus src gene product pp60src inactivate tyrosine protein kinase activity," <i>Mol. Cell. Biol.</i> 4:862-866, American Society for Microbiology (1984)

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>26</u>	Gerard, G.F. et al., "cDNA synthesis by cloned Moloney murine leukemia virus reverse transcriptase lacking Rnase H activity," <i>Focus</i> 11:66-69, Bethesda Research Laboratories (1989)	
AS	<u>26</u>	Houdebine, L.-M., "Synthesis of DNA complementary to the mRNAs for milk proteins by E. coli DNA polymerase I," <i>Nuc. Acids Res.</i> 3:615-630, IRL Press Ltd. (1976)	
AT	<u>26</u>	Ivanoff, L.A. et al., "Expression and site-specific mutagenesis of the poliovirus 3C protease in <i>Escherichia coli</i> ," <i>Proc. Natl. Acad. Sci. USA</i> 83:5392-5396, National Academy of Sciences (1986)	

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	27	Joyce, C.M. et al., "Construction of a plasmid that overproduces the large proteolytic fragment (Klenow fragment) of DNA polymerase I of Escherichia coli," Proc. Natl. Acad. Sci. USA 80:1830-1834, National Academy of Sciences (1983)
	AS	27	Voordouw, G. et al., "Site-directed mutagenesis of the small subunit of ribulose-1,5-bisphosphate carboxylase/oxygenase from Anacystis nidulans," Eur. J. Biochem. 163:591-598, Springer (1987)
	AT		

EXAMINER	DATE CONSIDERED
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Fourth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Fourth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Third Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. Except for document AC1, which was submitted in parent U.S. Application No. 09/220,329, copies of the cited documents were cited or submitted in parent U.S. Application No. 08/798,458. Thus, copies of the documents are not enclosed.

Document AR51, listed on the attached PTO-1449, is a copy of a letter dated December 10, 1999, from the ATCC regarding ATCC deposit no. 67555. Applicants submit that a deposit is not necessary to enable the present invention.

Applicants wish to bring to the attention of the Examiner the following information.

In August of 1997, Applicants' litigation counsel (Fulbright & Jaworski L.L.P.) served upon Stephen P. Goff a subpoena which required Dr. Goff's appearance at a deposition. The subpoena also required that Dr. Goff produce documents which referred to reverse transcriptase having reduced RNase H activity, including, for example, laboratory notebooks and other documents evidencing his conception and/or reduction to practice of reverse transcriptase having reduced RNase H activity (See document AS50). Pursuant to the subpoena, Dr. Goff produced

certain laboratory notebooks and other documents, and on December 19, 1997, Applicants' litigation counsel took Dr. Goff's deposition. The transcript of the deposition and/or Dr. Goff's notebooks may contain information which is material to the prosecution of the present application. However, the transcripts and notebooks are protected from disclosure by a court order (See document AT50). Accordingly, in the absence of permission from Columbia University, Dr. Goff's employer, the transcripts and notebooks cannot be disclosed to the U.S. Patent and Trademark Office without violating the court order.

Fulbright & Jaworski L.L.P. contacted counsel of Columbia University and requested permission for Applicants to disclose the transcript and notebooks to the U.S. Patent and Trademark Office. Columbia University refused to give such permission. Applicants submit that they have complied with their duty of disclosure to the full extent allowed by the law.

Applicants also wish to direct the attention of the Examiner to Interference No. 103,140 which was between an application of Goff (07/877,264) and a parent application of Kotewicz *et al.* (07/825,260, which corresponds to U.S. Patent No. 5,405,776).

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

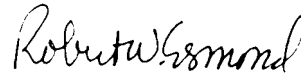
This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Fourth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449 FOURTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
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	AC1	6,063,608	05/16/2000	Kotewicz et al.	435	194	02/10/1997
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL1	WO 86/06741	11/20/1986	WIPO			Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR		
	AS		
	AT	27	Copeland, T.D. et al., "Amino- and Carboxyl-Terminal Sequence of Moloney Murine Leukemia Virus Reverse Transcriptase," Virology 143:676-679, Academic Press, Inc. (1985).

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>28</u>	Crouch, R. and Dirksen, M.-L., "Ribonucleases H", in <i>Nucleases</i> , Linn, S. and Roberts, R., eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pp 211-241 (1982).
	AS	<u>28</u>	Freeman-Wittig, M.-J. et al., "Differential Effects of Captan on DNA Polymerase and Ribonuclease H Activities of Avian Myeloblastosis Virus Reverse Transcriptase," <i>Biochemistry</i> 25:3050-3055, American Chemical Society (1986).
	AT	<u>28</u>	Freeman-Wittig, M.-J. et al., "Captan binding to avian myeloblastosis virus reverse transcriptase and its effect on RNase H activity," <i>Mol. Cell. Biochem.</i> 94:9-17, Kluwer Academic Publishers (1990).

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>29</u>	Gerard, G., "Comparison of cDNA Synthesis by Avian and Cloned Murine Reverse Transcriptase," <i>Focus</i> 7:1-3, Bethesda Research Laboratories (1985).	
AS	<u>29</u>	Gerard, G. et al., "cDNA Synthesis by Moloney Murine Leukemia Virus RNase H-Minus Reverse Transcriptase Possessing Full DNA Polymerase Activity," <i>Focus</i> 14:91-93, Bethesda Research Laboratories (1994)	
AT	<u>29</u>	Goff, S.P., "Genetic and Biochemical Approach to the Study of Retroviral Replication", Abstract from the 7 <sup>th</sup> Annual DNA Congress, San Francisco, CA (March 1987).	

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>30</u>	Grandgenett, D. et al., "Activation of an $Mg^{++}$ -Dependent DNA Endonuclease of Avian Myeloblastosis Virus $\alpha\beta$ DNA Polymerase by In Vitro Proteolytic Cleavage," <i>J. Virology</i> 33:264-271, American Society for Microbiology (1980).
	AS	<u>30</u>	Grandgenett, D. et al., "Structural Characterization of the Avian Retrovirus Reverse Transcriptase and Endonuclease Domains," <i>J. Biol. Chem.</i> 260:8243-8249, American Society of Biological Chemists, Inc. (1985).
	AT	<u>30</u>	Green, M. and Gerard, G., "RNA-Directed DNA Polymerase-Properties and Functions in Oncogenic RNA Viruses and Cells," <i>Progress in Nucleic Acid Research and Molecular Biology</i> 14:188-334, Academic Press, Inc. (1974).

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>31</u>	Hansen, J. et al., "Identification and characterization of HIV-specific RNase H by monoclonal antibody," <i>EMBO J.</i> 7:239-243, IRL Press Ltd. (1988).
	AS	<u>31</u>	Hizi, A. et al., "Expression of soluble, enzymatically active, human immunodeficiency virus reverse transcriptase in <i>Escherichia coli</i> and analysis of mutants," <i>Proc. Natl. Acad. Sci. USA</i> 85:1218-1222, National Academy of Sciences (1988).
	AT	<u>31</u>	Hizi, A. et al., "The Effects of Cysteine Mutations on Reverse Transcriptases of Human Immunodeficiency Virus Types 1 and 2," <i>J. Biol. Chem.</i> 267:1293-1297, American Society for Biochemistry and Molecular Biology, Inc. (1992).

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	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>32</u>	Holmes, M. H., "Elimination of Unwanted Restriction Sites from a Plasmid Bearing the Reverse Transcriptase Gene of Moloney Murine Leukemia Virus," University of Maryland, Baltimore County, MD, October 6, 1986.
	AS	<u>32</u>	Hostomsky, S. et al., "Ribonucleases H," in Nucleases, 2 <sup>nd</sup> ed., Linn, S. and Roberts, R., eds. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 341-376 (1993).
	AT	<u>32</u>	Jacobsen, H. et al., "The N-Terminal Amino-Acid Sequences of DNA Polymerase I from Escherichia coli and of the Large and the Small Fragments Obtained by a Limited Proteolysis," Eur. J. Biochem. 45:623-627, Springer (1974).

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	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>33</u>	Katayanagi, K. et al., "Crystal Structures of Ribonuclease HI Active Site Mutants from <i>Escherichia coli</i> ," <i>J. Biol. Chem.</i> 268:22092-22099, American Society for Biochemistry and Molecular Biology, Inc. (1993).
	AS	<u>33</u>	Klenow, H. and Henningsen, "Selective Elimination of the Exonuclease Activity of the Deoxyribonucleic Acid Polymerase from <i>Escherichia coli</i> B by Limited Proteolysis," <i>Proc. Natl. Acad. Sci. USA</i> , 65:168-175, National Academy of Sciences (1970).
	AT	<u>33</u>	Gerard, G., Inhibition of SUPERScript II Reverse Transcriptase by Common Laboratory Chemicals, Documents regarding CAT Transcription Detection and SuperScript RNase H Reverse Transcriptase brochure, from <i>Life Technologies, Inc.</i> v. Clontech Laboratories, Inc., U.S. District Court for the District of Maryland Southern Division, Civil Action No. AW96-4080, LTX18287- LTX18318, and LTX18321- LTX18344.

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>34</u>		Margalith, M. et al., "Differential inhibition of DNA polymerase and RNase H activities of the reverse transcriptase by phosphonoformate," <i>Mol. Cell. Biochem.</i> 43:97-103, Martinus Nijhoff/ Dr. W. Junk Publishers (1982).
AS	<u>34</u>		Mizrahi, V. et al., "Recombinant HIV-1 Reverse Transcriptase: Purification, Primary Structure, and Polymerase/Ribonuclease H Activities," <i>Arch. Biochem. Biophys.</i> 273:347-358, Academic Press, Inc. (1989).
AT	<u>34</u>		Modak, M.J. and Marcus, S.L., "Purification and Properties of Rauscher Leukemia Virus DNA Polymerase and Selective Inhibition of Mammalian Viral Reverse Transcriptase by Inorganic Phosphate," <i>J. Biol. Chem.</i> 252:11-19, American Society of Biological Chemists, Inc. (1977).
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>35</u>	Nakamura, H. et al., "Structural models of ribonuclease H domains in reverse transcriptase from retroviruses," <i>Nucl. Acids Res.</i> 19:1817-1823, Oxford University Press (1991).
	AS	<u>35</u>	Prasad, V. and Goff, S., "Linker insertion mutagenesis of the human immunodeficiency virus reverse transcriptase expressed in bacteria: Definition of the minimal polymerase domain," <i>Proc. Natl. Acad. Sci. USA</i> 86:3104-3108, National Academy of Sciences (1989).
	AT	<u>35</u>	Roth, M. et al., "Purification and Characterization of Murine Retroviral reverse Transcriptase Expressed in <i>Escherichia coli</i> ," <i>J. Biol. Chem.</i> 260:9326-9335, American Society of Biological Chemists, Inc. (1985).

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>36</u>	Schatz, O. et al., "Point mutations in conserved amino acid residues within the C-terminal domain of HIV-1 reverse transcriptase specifically repress RNase H function," <i>FEBS Lett.</i> 257:311-314, North-Holland Press (1989).
	AS	<u>36</u>	Schatz, O. et al., "Inactivation of the RNase H Domain of HIV-1 Reverse Transcriptase Blocks Viral Infectivity," <i>Adv. Appl. Biotech. Series 7</i> :293-303, Gulf Publishing (1989)
	AT	<u>36</u>	Skalka and Goff, S. eds., <i>Reverse Transcriptase</i> , Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1993).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>37</u>	Tanese, M. and Goff, S., "Domain Structure of the Moloney Murine Leukemia Virus Reverse Transcriptase: Mutational Analysis and Separate Expression of the DNA Polymerase and RNase H Activities," <i>Proc. Natl. Acad. Sci. USA</i> 85:1777-1781, National Academy of Sciences (1988).
	AS	<u>37</u>	Telesnitsky, A. et al., "Defects in Moloney Murine Leukemia Virus Replication Caused by a Reverse Transcriptase Mutation Modeled on the Structure of <i>Escherichia coli</i> RNase H," <i>J. Virology</i> 66:615-622, American Society for Microbiology (1992).
	AT	<u>37</u>	Tisdale, M. et al., "Mutations within the RNase H domain of human immunodeficiency virus type 1 reverse transcriptase abolish virus infectivity," <i>J. General Virology</i> 72:59-66, Society for General Microbiology (1991).
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>38</u>	Varmus, H. and Swanstrom, R., "Replication of Retroviruses," in <i>Molecular Biology of Tumor Viruses, RNA Tumor Viruses 2<sup>nd</sup> ed.</i> , Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 369-512 (1982).
	AS	<u>38</u>	Zhan, X. et al., "The Isolated RNase H Domain of Murine Leukemia Virus Reverse Transcriptase," <i>J. Biol. Chem.</i> 272:22023-22039, American Society for Biochemistry and Molecular Biology, Inc. (1997).
	AT	<u>38</u>	"Defendant's Notice Pursuant to 35 U.S.C. §282," from <i>Life Technologies, Inc. v. Clonetech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland Southern Division, Civil Action No. AW96-4080, pp. 1-8.

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>39</u>	"Transcript of Motions Hearing Before the Honorable Alexander Williams, Jr., United States District Judge," dated July 13, 1999, pp.1-48 from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>39</u>	"Transcript of Motions Hearing Before the Honorable Alexander Williams, Jr., United States District Judge" (Direct examination of Michael Leslie Kotewicz), dated July 13, 1999, pp. 1-65, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AT	<u>39</u>	"Morning Session" (Direct examination of Michael Leslie Kotewicz, cross examination of Michael Leslie Kotewicz, redirect examination of Michael Leslie Kotewicz, recross examination of Michael Leslie Kotewicz, direct examination of Robert Esmond), dated July 14, 1999, pp. 66-163, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	40	"Afternoon Session" (Direct examination of Robert Esmond, cross examination of Robert Esmond, direct examination of Harry F. Manbeck, cross examination of Harry F. Manbeck, redirect examination of Harry F. Manbeck, direct examination of Gary Floyd Gerard), dated July 14, 1999, pp.164-259, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.	
AS	40	"Morning Session" (Direct examination of Gary Floyd Gerard, cross examination of Gary Floyd Gerard, redirect examination of Gary Floyd Gerard, recross examination of Gary Floyd Gerard, direct examination of James J. Champoux, cross examination of James J. Champoux, redirect examination of James J. Champoux), dated July 15, 1999, pp.260-352, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.	
AT	40	"Transcript of Motions Hearing Before the Honorable Alexander Williams, Jr., United States District Judge" (Decision of the court), dated July 16, 1999, pp. 423-451, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.	

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FORM PTO-1449 FOURTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>41</u>	Garnier, J. et al., "Analysis of the Accuracy and Implications of Simple Methods for Predicting the Secondary Structure of Globular Proteins," <i>J. Mol. Biol.</i> 120:97-120, Academic Press, Inc. (1978)
	AS	<u>41</u>	Gerard, G.F., "Chapter 1. Reverse Transcriptase," in <i>Enzymes of Nucleic Acid Synthesis and Modification, Volume I, DNA Enzymes</i> , Jacob, S.T., ed., CRC Press, Inc., Boca Raton, FL, pp. 1-38 (1983)
	AT	<u>41</u>	Grandgenett, D.P et al., "A Single Subunit from Avian Myeloblastosis Virus with Both RNA-Directed DNA Polymerase and Ribonuclease H Activity," <i>Proc. Natl. Acad. Sci. USA</i> 70:230-234, National Academy of Sciences (1973)

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>42</u>	Houts, G.E. et al., "Reverse Transcriptase from Avian Myeloblastosis Virus," J. Virol. 29:517-522, American Society for Microbiology (1979)
	AS	<u>42</u>	Kanaya, S. and R.J. Crouch, "Low Levels of RNase H Activity in <i>Escherichia coli</i> FB2 <i>rnh</i> Result from a Single-Base Change in the Structural Gene of RNase H," J. Bacteriol. 154:1021-1026, American Society for Microbiology (1983)
	AT	<u>42</u>	Moelling, K., "Characterization of Reverse Transcriptase and RNase H from Friend-Murine Leukemia Virus," Virology 62:46-59, Academic Press, Inc. (1974)

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>43</u>	Moelling, K., "Further Characterization of the Friend Murine Leukemia Virus Reverse Transcriptase-RNase H Complex," <i>J. Virol.</i> 18:418-425, American Society for Microbiology (1976)
	AS	<u>43</u>	Old, R.W. and S.B. Primrose, "Cloning cDNA by Homopolymer Tailing," in <i>Principles of Gene Manipulation, An Introduction to Genetic Engineering</i> , 2nd Ed., University of California Press, Los Angeles, CA, pp. 26-27 (1981)
	AT	<u>43</u>	Omer, C.A. and A.J. Fares, "Mechanism of Release of the Avian Retroviruses tRNA <sup>Phe</sup> Primer Molecule from Viral DNA by Ribonuclease H During Reverse Transcription," <i>Cell</i> 30:797-805, Massachusetts Institute of Technology (1982)

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	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>44</u>	Toh, H. et al., "Close structural resemblance between putative polymerase of a <i>Drosophila</i> transposable genetic element 17.6 and pol gene product of Moloney murine leukaemia virus," <i>EMBO J.</i> 4:1267-1272, IRL Press Ltd. (1985)
	AS	<u>44</u>	Varmus, H., "Mechanisms Involved in the Synthesis of Retroviral DNA," in <i>RNA Tumor Viruses</i> , Weiss, R. et al., eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp. 410-423 (1982)
	AT	<u>44</u>	Defendant's Exhibit No. 14, LTX32496 - LTX32502, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>45</u>	Defendant's Exhibit No. 50, LTX34776 - LTX34780, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>45</u>	Defendant's Exhibit No. 88, LTX277 - LTX281, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AT	<u>45</u>	Defendant's Exhibit No. 124, LTX35319 - LTX35320, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>46</u>	Defendant's Exhibit No. 136, LTX35341 - LTX35343, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>46</u>	Defendant's Exhibit No. 137, LTX35344 - LTX35345, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AT	<u>46</u>	Defendant's Exhibit No. 138, LTX35346 - LTX35348, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>47</u>	Defendant's Exhibit No. 237, LTX6408, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>47</u>	Defendant's Exhibit No. 238, LTX6409 - LTX6410, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AT	<u>47</u>	Defendant's Exhibit No. 259, LTX34739 - LTX34763, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>48</u>	Defendant's Exhibit No. 394, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
AS	<u>48</u>	Defendant's Exhibit No. 399, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
AT	<u>48</u>	Defendant's Exhibit No. 398, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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	APPLICANTS Kotewicz et al.	
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>49</u>	Defendant's Exhibit No. 397, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>49</u>	Defendant's Exhibit No. 396, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AT	<u>49</u>	Defendant's Exhibit No. 401, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.

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	AL						Yes No
	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>50</u>	Defendant's Exhibit No. 433, from <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080.
	AS	<u>50</u>	"Subpoena in a Civil Case" dated August 21, 1997, served upon Stephen P. Goff, <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , Civil Action No. AW 96-4080, U.S. District Court for the District of Maryland, Southern Division.
	AT	<u>50</u>	"Stipulation and Protective Order Re Confidential Documents of Non-Parties Columbia University and Dr. Stephen P. Goff," <i>Life Technologies, Inc. v. Clontech Laboratories, Inc.</i> , Civil Action No. AW 96-4080, U.S. District Court for the District of Maryland, Southern Division.

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AE	<u>51</u>	Letter from ATCC to Robert W. Esmond dated December 10, 1999.
	AS	<u>51</u>	Buiser, R.G., et al., "Requirements for the catalysis of strand transfer synthesis by retroviral DNA polymerases," <i>J. Biol. Chem.</i> 266:13103-13109, American Society for Biochemistry and Molecular Biology, Inc. (1991).
	AT	<u>51</u>	DeStefano, J.J., et al., "Polymerization and Rnase H activities of the reverse transcriptase from avian myeloblastosis, human immunodeficiency, and Moloney murine leukemia viruses," <i>J. Biol. Chem.</i> 266:7423-7431, American Society for Biochemistry and Molecular Biology, Inc. (1991)

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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	52	Goff, S.P., and Lebel, L.I., "Mutants of murine leukemia viruses and retroviral replication," <i>Biochim. Biophys. Acta</i> 907:93-123, Elsevier Science B.V. (1987)
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	AT		

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10 024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Fifth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Fifth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Fourth Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by or submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not

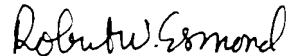
exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Fifth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600



FORM PTO-1449 <u>FIFTH SUPPLEMENTAL</u> <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 0942.049100B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR		
	AS	52	Life Technologies, Inc. v. Clontech Laboratories, Inc., Appeal 99-1550 (Fed. Cir. September 21, 2000)
	AT	52	"Complaint for Declaratory Judgment," dated June 22, 2000, from Clontech Laboratories, Inc. v. Life Technologies, Inc., U.S. District Court, Southern District of Maryland, Civil Action No. AW 00 CV 1879

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Kotewicz *et al.*

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Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Sixth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Sixth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Fifth Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by or submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search

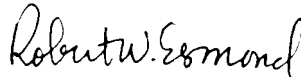
has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Sixth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Date: March 5, 2003

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FORM PTO-1449  SIXTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AE	<u>53</u>	Barr, P.J., et al., "Expression of Active Human Immunodeficiency Virus Reverse Transcriptase in <i>Saccharomyces Cerevisiae</i> ," <i>Bio/Technology</i> 5:486-489, Nature Publishing Company (May 1987).
	AS	<u>53</u>	Bathurst, I.C., et al., "Characterization of the Human Immunodeficiency Virus Type-1 Reverse Transcriptase Enzyme Produced in Yeast," <i>Biochem. Biophys. Res. Commun.</i> 171:589-595, Academic Press, Inc. (1990).
	AT	<u>53</u>	Champoux, J.J., "Roles of Ribonuclease H in Reverse Transcription," in <i>Reverse Transcriptase</i> , Ch. 6, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 103-117 (1993).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>54</u>	Farmerie, W.G., et al., "Expression and Processing of the AIDS Virus Reverse Transcriptase in Escherichia coli," <i>Science</i> 236:305-308, Association for the Advancement of Science (1987).
	AS	<u>54</u>	Georgiadis, M., et al., "Mechanistic implications from the structure of a catalytic fragment of Moloney murine leukemia virus reverse transcriptase," <i>Structure</i> 3:879-892, Current Biology LTD., (1995).
	AT	<u>54</u>	Golomb, M. and Grandgenett, D.P., "Endonuclease Activity of Purified RNA-directed DNA Polymerase from Avian Myeloblastosis Virus," <i>J. Biol. Chem.</i> 254:1606-1613, American Society of Biological Chemists, Inc., (1979).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>55</u>	Hansen, J., et al., "RNase H Activity Associated with Bacterially Expressed Reverse Transcriptase of Human T-cell Lymphotropic Virus III/Lymphadenopathy-associated Virus," <i>J. Biol. Chem.</i> 262:12393-12396, American Society for Biochemistry and Molecular Biology, (1987).
	AS	<u>55</u>	Hansen, J., et al., "Identification and characterization of HIV-specific RNase H by monoclonal antibody," <i>EMBO J.</i> 7:239-243, IRL Press Limited (1988).
	AT	<u>55</u>	Houts, G.E., et al., "Reverse Transcriptase from Avian Myeloblastosis Virus," <i>J. Virol.</i> 29:517-522, American Society for Microbiology (1979).

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AR	<u>56</u>	Huber, H.E., et al., "Human Immunodeficiency Virus 1 Reverse Transcriptase," <i>J. Biol. Chem.</i> 264:4669-4678, American Society for Biochemistry and Molecular Biology, Inc. (1989).	
AS	<u>56</u>	Inouye, S., and Inouye, M., "Bacterial Reverse Transcriptase," in <i>Reverse Transcriptase</i> , Ch. 17, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 391-410 (1993).	
AT	<u>56</u>	Kacian, D.L. and Myers, J.C., "Synthesis of extensive, possibly complete, DNA copies of poliovirus RNA in high yields and at high specific activities," <i>Proc. Natl. Acad. Sci. USA</i> 73:2191-2195, National Academy of Sciences USA (1976).	

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	AR	<u>57</u>	Larder, B., et al., "Site-Specific mutagenesis of AIDS virus reverse transcriptase," Nature 327:716-717, Macmillan Publishers Ltd. (1987).
	AS	<u>57</u>	Larder, B., et al., "AIDS virus reverse transcriptase defined by high level expression in <i>Escherichia coli</i> ," EMBO J. 6:3133-3137, IRL Press Limited (1987).
	AT	<u>57</u>	Le Grice, S., "Human Immunodeficiency Virus Reverse Transcriptase," in Reverse Transcriptase, Skalka, A.M. and Goff, S.P., eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 163-191 (1993).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>58</u>	Levin, J.G., et al., "Functional Organization of the Murine Leukemia Virus Reverse Transcriptase: Characterization of a Bacterially Expressed AKR DNA Polymerase Deficient in RNase H Activity," <i>J. Virol.</i> 62:4376-4380, American Society for Microbiology (1988).
	AS	<u>58</u>	Lightfoote, M.M., et al., "Structural Characterization of Reverse Transcriptase and Endonuclease Polypeptides of the Acquired Immunodeficiency Syndrome Retrovirus," <i>J. Virol.</i> 60:771-775, American Society for Microbiology (1986).
	AT	<u>58</u>	Lori, F., et al., "Enzymatically Active Forms of Reverse Transcriptase of the Human Immunodeficiency Virus," <i>AIDS Res. Hum. Retroviruses</i> 4:393-398, Mary Ann Leibert, Inc., Publishers (1988).

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AR	<u>59</u>	Lowe, D.M., et al., "HIV-1 Reverse Transcriptase: Crystallization and Analysis of Domain Structure by Limited Proteolysis," <i>Biochemistry</i> 27:8884-8889, American Chemical Society (1988).
AS	<u>59</u>	Mizrahi, V., et al., "Mutagenesis of the Conserved Aspartic Acid 443, Glutamic Acid 478, Asparagine 494, and Aspartic Acid 498 Residues in the Ribonuclease H Domain of p66/p51 Human Immunodeficiency Virus Type 1 Reverse Transcriptase," <i>J. Biol. Chem.</i> 269:19245-19249, American Society for Biochemistry and Molecular Biology, Inc. (1994).
AT	<u>59</u>	Müller, B., et al., "Co-expression of the Subunits of the Heterodimer of HIV-1 Reverse Transcriptase in <i>Escherichia coli</i> ," <i>J. Biol. Chem.</i> 264:13975-13978, American Society for Biochemistry and Molecular Biology, Inc. (1989).

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AR	60	Myers, J.C., et al., "Synthesis of full-length DNA copies of avian myeloblastosis virus RNA in high yields," <i>Proc. Natl. Acad. Sci. USA</i> 74:2840-2843, National Academy of Sciences USA (1977).
AS	60	Myers, J.C., et al., RNA primer used in synthesis of anticomplementary DNA by reverse transcriptase of avian myeloblastosis virus," <i>Proc. Natl. Acad. Sci. USA</i> 77:1316-1320, National Academy of Sciences USA (1980).
AT	60	Najmudin, S., et al., "Crystal Structures of an N-terminal Fragment from Moloney Murine Leukemia Virus Reverse Transcriptase Complexed with Nucleic Acid: Functional Implications for Template-primer Binding to the Fingers Domain," <i>J. Mol. Biol.</i> 296:613-632, Academic Press, Inc. (2000).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>61</u>	Prasad, V.R., "Genetic Analysis of Retroviral Reverse Transcriptase Structure and Function," in <i>Reverse Transcriptase</i> , Skalka, A.M. and Goff, S.P., eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 135-162 (1993).
AS	<u>61</u>	Reardon, J., et al., "Human Immunodeficiency Virus Reverse Transcriptase," <i>J. Biol. Chem.</i> 266:14128-14134, American Society for Biochemistry and Molecular Biology, Inc. (1991).
AT	<u>61</u>	Schatz, O., et al., "HIV-1 RT-associated ribonuclease H displays both endonuclease and 3' → 5' exonuclease activity," <i>EMBO J.</i> 9:1171-1176, IRL Press Limited (1990).

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AR	62	Schiff, R.D. and Grandgenett, D.P., "Virus-Coded Origin of a 32,000-Dalton Protein from Avian Retrovirus Cores: Structural Relatedness of p32 and the $\beta$ Polypeptide of the Avian Retrovirus DNA Polymerase," <i>J. Virol.</i> 28:279-291, American Society for Microbiology (1978).
AS	62	Skalka, A.M., "Endonuclease Activity Associated with Reverse Transcriptase of Avian Sarcoma-Leukosis Viruses," in <i>Reverse Transcriptase</i> , Ch. 10, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 193-204 (1993).
AT	62	Srivastava, A. and Modak, M.J., "Reverse Transcriptase-Associated RNase H. Part IV. Pyrophosphate does not inhibit RNase activity of AMV DNA polymerase," <i>Biochem. Biophys. Res. Commun.</i> 91:892-899, Academic Press, Inc. (1979).

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AR	<u>63</u>	Starnes, M.C., et al., "Enzyme Activity Gel Analysis of Human Immunodeficiency Virus Reverse Transcriptase," J. Biol. Chem. 263:5132-5134, American Society for Biochemistry and Molecular Biology, Inc. (1988).	
AS	<u>63</u>	Takatsuji, H., et al., "Expression of cauliflower mosaic virus reverse transcriptase in yeast," Nature 319:240-243, Macmillan Publishers Ltd. (1986).	
AT	<u>63</u>	Tanese, N., et al., "Expression of Reverse Transcriptase Activity of Human T-Lymphotropic Virus Type III (HTLV-III/LAV) in Escherichia coli," J. Virol. 59:743-745, American Society for Microbiology (1986).	

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AR	<u>64</u>	Thimmig, R.L. and McHenry, C.S., "Human Immunodeficiency Virus Reverse Transcriptase," J. Biol. Chem. 268:16528-16536, American Society for Biochemistry and Molecular Biology, Inc. (1993).	
AS	<u>64</u>	Tisdale, M., et al., "Characterization of Human Immunodeficiency Virus Type 1 Reverse Transcriptase by Using Monoclonal Antibodies: Role of the C Terminus in Antibody Reactivity and Enzyme Function," J. Virol. 62:3662-3667, American Society for Microbiology (1988).	
AT	<u>64</u>	Tisdale, M., et al., "Structural characterization of HIV reverse transcriptase: A target for the design of specific virus inhibitors," J. Antimicrobiol. Chemother. 23 Suppl A :47-54, Academic Press, Inc. (1989).	

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AR	65	Van Beveren, C. and Goulian, M., "Optimal Conditions for Synthesis of Long Complementary DNA Product with Moloney Murine Leukemia Virus," J. Virol. 30:951-954, American Society for Microbiology (1979).
AS	65	Veronese, F., et al., "Characterization of Highly Immunogenic p66/p51 as the Reverse Transcriptase of HTLV-III/LAV," Science 231:1289-1291, Association for the Advancement of Science (1986).
AT	65	Volkman, S., et al., "Enzymatic Analysis of Two HIV-1 Reverse Transcriptase Mutants with Mutations in Carboxyl-terminal Amino Acid Residues Conserved among Retroviral Ribonucleases H," J. Biol. Chem. 268:2674-2683, American Society for Biochemistry and Molecular Biology, Inc. (1993).

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FORM PTO-1449  SIXTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AP	<u>66</u>	Wöhrl, B.M., et al., "Kinetic Analysis of Four HIV-1 Reverse Transcriptase Enzymes Mutated in the Primer Grip Region of p66," J. Biol. Chem. 272:17581-17587, American Society for Biochemistry and Molecular Biology, Inc. (1997).
	AS	<u>66</u>	"Complaint," dated June 29, 2000, from Life Technologies, Inc. v. Promega Corporation, U.S. District Court, Western District of Wisconsin, Civil Action No. 00C 0407 C.
	AT	<u>66</u>	"Answer," dated October 17, 2000, from Life Technologies, Inc. v. Promega Corporation, U.S. District Court, Western District of Wisconsin, Civil Case No. 00-C-0407-C.

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FORM PTO-1449  SIXTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049111B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	67	"Complaint," dated June 29, 2000, from Life Technologies, Inc. v. Stratagene Holding Corp., Stratagene, Inc., and Biocrest Manufacturing, L.P., U.S. District Court, District of Delaware, Civil Action No. 00-620.	
AS	67	"Answer," dated November 30, 2000, from Life Technologies, Inc. v. Stratagene Holding Corp., Stratagene, Inc., and Biocrest Manufacturing, L.P., U.S. District Court, District of Delaware, Civil Action No. 00-620.	
AT			

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Seventh Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Seventh Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Sixth Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited and submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings

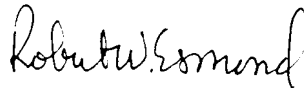
purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that was cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Seventh Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

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FORM PTO-1449  SEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR			
AS			
AT	67	Chattopadhyay, D., et al., "Resolution of Microheterogeneity Associated with Recombinant HIV-1 Heterodimeric Reverse Transcriptase," <i>Protein Expression and Purification</i> 3:151-159, Academic Press, Inc. (1992)	

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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>68</u>	Gerard, G.F., "Synthesis of High Specific Activity cDNA," Focus 10:12-13, Life Technologies, Inc. (1988)
	AS	<u>68</u>	Hizi, A. and Joklik, W.K., "RNA-dependent DNA Polymerase of Avian Sarcoma Virus B77," J. Biol. Chem. 252:2281-2289, The American Society of Biological Chemists, Inc. (1977)
	AT	<u>68</u>	Myers, J.C. and Spiegelman, S., "Sodium pyrophosphate inhibition of RNA•DNA hybrid degradation by reverse transcriptase," Proc. Natl. Acad. Sci. USA 75:5329-5333, Proceedings of the National Academy of Sciences (1978)

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FORM PTO-1449  SEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE-MTT	APPLICATION NO. 10/024,131
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	AN						Yes No
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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	69	Verma, I.M., "Studies on Reverse Transcriptase of RNA Tumor Viruses. III. Properties of Purified Moloney Murine Leukemia Virus DNA Polymerase and Associated RNase H," J. Virol. 15:843-854, American Society for Microbiology (1975)
AS	69	Wang, L.-H. And Duesberg, P.H., "DNA Polymerase of Murine Sarcoma-Leukemia Virus: Lack of Detectable RNase H and Low Activity With Viral RNA and Natural DNA Templates," J. Virol. 12:1512-1521, American Society for Microbiology (1973)
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EXAMINER

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10:024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Eighth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering of documents in this Eighth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Seventh Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application.

The Examiner's attention is directed to the following co-pending U.S. Patent Applications, which are directed to related technical subject matter:

U.S. Patent Application No. 09/845,157, filed May 1, 2001, cited herein as Document **AS99**.

U.S. Patent Application No. 09/808,124, filed March 15, 2001, cited herein as Document **AT99**.



U.S. Patent Application No. 09 902,741, filed July 12, 2001, cited herein as Document  
**AR100.**

All documents were cited and submitted to the Office in Application No. 09/220,329,  
filed December 24, 1998.

The identification of these U.S. Patent Applications is not to be construed as a waiver of  
secrecy as to those applications now or upon issuance of the present application as a patent. The  
Examiner is respectfully requested to consider the cited applications and the art cited therein  
during examination.

Where the publication date of a listed document does not provide a month of publication,  
the year of publication of the listed document is sufficiently earlier than the effective U.S. filing  
date and any foreign priority date so that the month of publication is not in issue. Applicants  
have listed publication dates on the attached PTO-1449 based on information presently available  
to the undersigned. However, the listed publication dates should not be construed as an  
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Applicants reserve the right to establish the patentability of the claimed invention over  
any of the information provided herewith, and/or to prove that this information may not be prior  
art, and/or to prove that this information may not be enabling for the teachings purportedly  
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This statement should not be construed as a representation that a search has been made,  
or that information more material to the examination of the present patent application does not  
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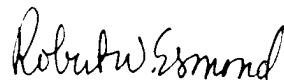
cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

This Eighth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

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Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449 <u>EIGHTH SUPPLEMENTAL</u> <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR		
	AS		
	AT	69	Allain, B. et al., "CIS Elements and Trans-acting Factors required for Minus Strand DNA Transfer during Reverse Transcription of the Genomic RNA of Murine Leukemia Virus," J. Mol. Biol. 277:225-235, Academic Press Limited (March 1998).

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FORM PTO-1449  <u>EIGHTH SUPPLEMENTAL</u> <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	70	Arendes, J. et al., "A Mutation in the <i>rnh</i> -locus of <i>Escherichia coli</i> Affects the Structural Gene for RNase H," <i>J. Biol. Chem.</i> 257:4719-4722, The American Society of Biological Chemists, Inc. (1982).
	AS	70	Arion, D. et al., "The K65R Mutation Confers Increased DNA Polymerase Processivity to HIV-1 Reverse Transcriptase," <i>J. Biol. Chem.</i> 271:19860-19864, The American Society for Biochemistry and Molecular Biology, Inc. (1996).
	AT	70	Arnold, E. et al., "Structure of HIV-1 reverse transcriptase/DNA complex at 7 Å resolution showing active site locations," <i>Nature</i> 357:85-89, Macmillan Publishers Ltd. (1992).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>71</u>	Bahar, I., "Collective Motions in HIV-1 Reverse Transcriptase: Examination of Flexibility and Enzyme Function," <i>J. Mol. Biol.</i> 285:1023-1037, Academic Press (January 1999).
AS	<u>71</u>	Basu, S. et al., "Sulphydryl groups in the template-primer-binding domain of murine leukaemia virus reverse transcriptase," <i>Biochem. J.</i> 296:577-583, The Biochemical Society (1993).
AT	<u>71</u>	Beard, W.A. et al., "Structure/Function Studies of Human Immunodeficiency Virus Type 1 Reverse Transcriptase," <i>J. Biol. Chem.</i> 269:28091-28097, American Society for Biochemistry and Molecular Biology (1994).

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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>72</u>	Ben-Artzi, H. et al., "Characterization of the double stranded RNA dependent RNase activity associated with recombinant reverse transcriptases," Nucl. Acids Res. 20:5115-5118, Oxford University Press (1992).
AS	<u>72</u>	Blain, S.W. and Goff, S.P., "Effects on DNA Synthesis and Translocation Caused by Mutations in the RNase H Domain of Moloney Murine Leukemia Virus Reverse Transcriptase," J. Virol. 69:4440-4452, American Society for Microbiology (1995).
AT	<u>72</u>	Blain, S.W. and Goff, S.P., "Differential Effects of Moloney Murine Leukemia Virus Reverse Transcriptase Mutations on RNase H Activity in Mg <sup>++</sup> and Mn <sup>++</sup> ," J. Biol. Chem. 271:1448-1454, The American Society for Biochemistry and Molecular Biology, Inc. (1996).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>73</u>	Caliendo, A.M. et al., "Effects of Zidovudine-Selected Human Immunodeficiency Virus Type 1 Reverse Transcriptase Amino Acid Substitutions on Processive DNA Synthesis and Viral Replication," <i>J. Virol.</i> 70:2146-2153, American Society for Microbiology (1996).
AS	<u>73</u>	Carl, P.L. et al., "Isolation and Mapping of a Mutation in <i>Escherichia coli</i> with Altered Levels of Ribonuclease H," <i>J. Bacteriol.</i> 144:28-35, American Society for Microbiology (1980).
AT	<u>73</u>	Carmichael, G.G. and McMaster, G.K., "The Analysis of Nucleic Acids in Gels Using Glyoxal and Acridine Orange," <i>Meth. Enzymol.</i> 65:380-391, Academic Press, Inc. (1980).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	74	Catucci, M. et al., "Development and Significance of the HIV-1 Reverse Transcriptase M184V Mutation During Combination Therapy With Lamivudine, Zidovudine, and Protease Inhibitors," <i>J. Acquir. Immune Defic. Syndr.</i> 21:203-208, Lippincott Williams & Wilkins, Inc. (July 1999).
AS	74	Chen, Y. and Marion, P.L., "Amino Acids Essential for RNase H Activity of Hepadnaviruses Are Also Required for Efficient Elongation of Minus-Strand Viral DNA," <i>J. Virol.</i> 70:6151-6156, American Society for Microbiology (1996).
AT	74	Chowdhury, K. et al., "Elucidation of the Role of Arg 110 of Murine Leukemia Virus Reverse Transcriptase in the Catalytic Mechanism: Biochemical Characterization of Its Mutant Enzymes," <i>Biochemistry</i> 35:16610-16620, American Chemical Society (1996).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>75</u>	DeStefano, J.J. et al., "Requirements for Strand Transfer between Internal Regions of Heteropolymer Templates by Human Immunodeficiency Virus Reverse Transcriptase," <i>J. Virol.</i> 66:6370-6378, American Society for Microbiology (1992).
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	AT	<u>75</u>	Ditta, G. et al., "Broad host range DNA cloning system for gram-negative bacteria: Construction of a gene bank of <i>Rhizobium meliloti</i> ," <i>Proc. Natl. Acad. Sci. USA.</i> 77:7347-7351, National Academy of Sciences (1980).

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FORM PTO-1449 EIGHTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AM						Yes No
	AN						Yes No
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	AR	<u>76</u>	Drosopoulos, W.C. and Prasad, V.R., "Increased Polymerase Fidelity of E89G, a Nucleoside Analog-Resistant Variant of Human Immunodeficiency Virus Type 1 Reverse Transcriptase," J. Virol. 70:4834-4838, American Society for Microbiology (1996).
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	AT	<u>76</u>	Fontaine, E. et al., "Fast Genotypic Detection of Drug Resistance Mutations in the HIV-1 Reverse Transcriptase Gene of Treatment-Naive Patients," J. Hum. Virol. 1:451-456, Lippincott Williams & Wilkins (November-December 1998).

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AR	<u>78</u>	Georgiadis, M.M. et al., "Mechanistic implications from the structure of a catalytic fragment of Moloney murine leukemia virus reverse transcriptase," Structure 3:879-892, Current Biology Ltd. (1995).
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AT	<u>78</u>	Gerard, G.F. and D'Alessio, J.M., "Reverse Transcriptase (EC 2.7.7.49): The Use of Cloned Moloney Murine Leukemia Virus Reverse Transcriptase to Synthesize DNA from RNA," in Methods in Molecular Biology, vol. 16: Enzymes of Molecular Biology, Burrell, M.M., ed., Humana Press Inc., Totowa, N.J., pp. 73-93 (1993).

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AT	<u>80</u>	Götte, M. et al., "The M184V Mutation in the Reverse Transcriptase of Human Immunodeficiency Virus Type 1 Impairs Rescue of Chain-Terminated DNA Synthesis," <i>J. Virol.</i> 74:3579-3585, American Society for Microbiology (April 2000).

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	AR	<u>81</u>	Gottesman, M.E. et al., "Transcription Antitermination by Bacteriophage Lambda N Gene Product," <i>J. Mol. Biol.</i> 140:57-75, Academic Press Inc. (1980).
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AR	<u>82</u>	Hafkemeyer, P. et al., "HP 0.35, a cephalosporin degradation product is a specific inhibitor of lentiviral RNases H," <i>Nucl. Acids Res.</i> 19:4059-4065, Oxford University Press (1991).
AS	<u>82</u>	Han, L.-Y. et al., "Ribonuclease H Renaturation Gel Assay Using a Fluorescent-Labeled Substrate," <i>BioTechniques</i> 23:920-926, Eaton Publishing Co. (November 1997).
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	AR	<u>83</u>	Jaeger, J. et al., "The structure of HIV-1 reverse transcriptase complexed with an RNA pseudoknot inhibitor," <i>EMBO J.</i> 17:4535-4542, Oxford University Press (August 1998).
	AS	<u>83</u>	Jin, J. et al., "Analysis of the Role of Glutamine 190 in the Catalytic Mechanism of Murine Leukemia Virus Reverse Transcriptase," <i>J. Biol. Chem.</i> 274:20861-20868, The American Society for Biochemistry and Molecular Biology, Inc. (July 1999).
	AT	<u>83</u>	Kanaya, S. and Crouch, R.J., "DNA Sequence of the Gene Coding for <i>Escherichia coli</i> Ribonuclease H," <i>J. Biol. Chem.</i> 258:1276-1281, The American Society of Biological Chemists, Inc. (1983).

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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>84</u>	Kanaya, S. and Crouch, R.J., "Low Levels of RNase H Activity in <i>Escherichia coli</i> FB2 <i>rnh</i> Result from a Single-Base Change in the Structural Gene of RNase H," <i>J. Bacteriol.</i> 154:1021-1026, American Society for Microbiology (1983).
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>85</u>	Kaushik, N. et al., "Role of Glutamine 151 of Human Immunodeficiency Virus Type-1 Reverse Transcriptase in Substrate Selection As Assessed by Site-Directed Mutagenesis," <i>Biochemistry</i> 39:2912-2920, American Chemical Society (March 2000; published on the web 02/22/2000).
	AS	<u>85</u>	Keck, J.L., et al., "Activation/Attenuation Model for RNase H. A One-Metal Mechanism with Second-Metal Inhibition," <i>J. Biol. Chem.</i> 273:34128-34133, The American Society for Biochemistry and Molecular Biology, Inc. (December 1998).
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AR	<u>86</u>	Kern, G. et al., "Characterization of a folding intermediate from HIV-1 ribonuclease H," <i>Protein Sci.</i> 7:2164-2174, Cambridge University Press (October 1998).
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	AR	<u>87</u>	Larder, B.A. et al., "A Family of Insertion Mutations between Codons 67 and 70 of Human Immunodeficiency Virus Type 1 Reverse Transcriptase Confer Multinucleoside Analog Resistance," <i>Antimicrob. Agents Chemother.</i> 43:1961-1967, American Society for Microbiology (August 1999).
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>89</u>	Maxam, A.M. and Gilbert, W., "Sequencing End-Labeled DNA with Base-Specific Chemical Cleavages," <i>Meth. Enzymol.</i> 65:499-560, Academic Press, Inc. (1980).
	AS	<u>89</u>	McDonell, M.W. et al., "Analysis of Restriction Fragments of T7 DNA and Determination of Molecular Weights by Electrophoresis in Neutral and Alkaline Gels," <i>J. Mol. Biol.</i> 110:119-146, Academic Press, Inc. (1977)
	AT	<u>89</u>	Medrano, L. et al., "Sequence Analysis of the Polymerase Domain of HIV-1 Reverse Transcriptase in Naive and Zidovudine-Treated Individuals Reveals a Higher Polymorphism in $\beta$ -Helices as Compared with $\alpha$ -strands," <i>Virus Genes</i> 18:203-210, Kluwer Academic Publishers (June 1999).

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FORM PTO-1449  EIGHTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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AR	<u>90</u>	Messing, J., "New M13 Vectors for Cloning," <i>Meth. Enzymol.</i> 101:20-78, Academic Press, Inc. (1983).
AS	<u>90</u>	Misra, H.S. et al., "An Enzymatically Active Chimeric HIV-1 Reverse Transcriptase (RT) with the RNase-H Domain of Murine Leukemia Virus RT Exists as a Monomer," <i>J. Biol. Chem.</i> 273:9785-9789, The American Society for Biochemistry and Molecular Biology, Inc. (April 1998).
AT	<u>90</u>	Murante, R.S. et al., "Junction ribonuclease: An activity in Okazaki fragment processing," <i>Proc. Natl. Acad. Sci. USA.</i> 95:2244-2249, The National Academy of Sciences (March 1998).

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	AR	<u>91</u>	Nakamura, H. et al., "How does RNase H recognize a DNA-RNA hybrid?" <i>Proc. Natl. Acad. Sci. (USA)</i> 88:11535-11539, The National Academy of Sciences (1991).
	AS	<u>91</u>	Nishitani, H. et al., "Specific chromosomal sites enhancing homologous recombination in <i>Escherichia coli</i> mutants defective in RNase H," <i>Mol. Gen. Genet.</i> 240:307-314, Springer-Verlag (1993).
	AT	<u>91</u>	Oliveras, I. et al., "Second-Site Reversion of a Human Immunodeficiency Virus Type 1 Reverse Transcriptase Mutant That Restores Enzyme Function and Replication Capacity," <i>J. Virol.</i> 73:6293-6298, American Society for Microbiology (August 1999).

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AR	<u>92</u>	Patel, P.H. et al., "Insights into DNA Polymerization Mechanisms from Structure and Function Analysis of HIV-1 Reverse Transcriptase," <i>Biochemistry</i> 34:5351-5363, American Chemical Society (1995).	
AS	<u>92</u>	Peliska, J.A. and Benkovic, S.J., "Mechanism of DNA Strand Transfer Reactions Catalyzed by HIV-1 Reverse Transcriptase," <i>Science</i> 258:1112-1118, American Association for the Advancement of Science (1992).	
AT	<u>92</u>	Post, K. et al., "A Large Deletion in the Connection Subdomain of Murine Leukemia Virus Reverse Transcriptase or Replacement of the RNase H Domain with <i>Escherichia coli</i> RNase H Results in Altered Polymerase and RNase H Activities," <i>Biochemistry</i> 32:5508-5517, American Chemical Society (1993).	

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>93</u>	Precious, H.M. et al., "Multiple sites in HIV-1 reverse transcriptase associated with virological response to combination therapy," AIDS 14:31-36, Lippincott Williams & Wilkins (January 2000).
	AS	<u>93</u>	Richardson, C.C. et al., "Enzymatic Synthesis of Deoxyribonucleic Acid," J. Biol. Chem. 239:222-231, The American Society of Biological Chemists, Inc. (1964).
	AT	<u>93</u>	Rodgers, D.W. et al., "The structure of unliganded reverse transcriptase from the human immunodeficiency virus type 1," Proc. Natl. Acad. Sci. (USA) 92:1222-1226, The National Academy of Sciences (1995).

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AR	<u>94</u>	Sarafianos, S.G. et al., "Crystal structure of HIV-1 reverse transcriptase in complex with a polypurine tract RNA:DNA," <i>EMBO J.</i> 20:1449-1461, European Molecular Biology Organization (March 2001).
AS	<u>94</u>	Schultz, S.J. et al., "Polypurine Tract Primer Generation and Utilization by Moloney Murine Leukemia Virus Reverse Transcriptase," <i>J. Biol. Chem.</i> 274:34547-34555, The American Society for Biochemistry and Molecular Biology, Inc. (December 1999).
AT	<u>94</u>	Shirasawa, Y. et al., "Transdominant Inhibition of Moloney Murine Leukemia Virus Proliferation by Defective Mutants of Reverse Transcriptase," <i>J. Biochem.</i> 119:1070-1075, The Japanese Biochemical Society (1996).

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AR	<u>95</u>	Smith, C.M. et al, "Sequence Requirements for Removal of tRNA by an Isolated Human Immunodeficiency Virus Type 1 RNase H Domain," <i>J. Virol.</i> 72:6805-6812, American Society for Microbiology (August 1998).
AS	<u>95</u>	Smith, R.A. et al., "A New Point Mutation (P157S) in the Reverse Transcriptase of Human Immunodeficiency Virus Type 1 Confers Low-Level Resistance to (-)-β-2',3'-Dideoxy-3'-Thiacytidine," <i>Antimicrob. Agents Chemotherapy</i> 43:2077-2080, American Society for Microbiology (August 1999).
AT	<u>95</u>	Southern, E.M., "Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis," <i>J. Mol. Biol.</i> 98:503-517, Academic Press (1975).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>96</u>	Spedding, G. et al., "Inhibition of reverse transcriptases by flavonoids," Antiviral Res. 12:99-110, Elsevier Science Publishers B.V. (Biomedical Division) (1989).
	AS	<u>96</u>	Sugiura, W. et al., "Identification of Insertion Mutations in HIV-1 Reverse Transcriptase Causing Multiple Drug Resistance to Nucleoside Analogue Reverse Transcriptase Inhibitors," J. Hum. Virol. 2:146-153, Lippincott Williams & Wilkins, Inc. (May-June 1999).
	AT	<u>96</u>	Sun, D. et al., "Cloning, expression, and purification of a catalytic fragment of Moloney murine leukemia virus reverse transcriptase: Crystallization of nucleic acid complexes," Protein Sci. 7:1575-1582, Cambridge University Press (July 1998).

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	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>97</u>	Tanese, N. et al., "Abortive Reverse Transcription by Mutants of Moloney Murine Leukemia Virus Deficient in the Reverse Transcriptase-Associated RNase H Function," <i>J. Virol.</i> 65:4387-4397, American Society for Microbiology (1991).
	AS	<u>97</u>	Trentin, B. et al., "Human T-cell Leukemia Virus Type 1 Reverse Transcriptase (RT) Originates from the pro and pol Open Reading Frames and Requires the Presence of RT-RNase H (RH) and RT-RH-Integrase Proteins for its Activity," <i>J. Virol.</i> 72:6504-6510, American Society for Microbiology (August 1998).
	AT	<u>97</u>	Veal, G.J. et al., "Sequence-specific RNase H cleavage of gag mRNA from HIV-1 infected cells by an antisense oligonucleotide in vitro," <i>Nucl. Acids Res.</i> 26:5670-5675, Oxford University Press (December 1998).

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	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>98</u>	Yadav, P.N.S. et al., "A Computer-assisted Analysis of Conserved Residues in the Three-dimensional Structures of the Polymerase Domains of <i>Escherichia coli</i> DNA Polymerase I and HIV-1 Reverse Transcriptase," <i>J. Biol. Chem.</i> 269:716-720, The American Society for Biochemistry and Molecular Biology, Inc. (1994).
	AS	<u>98</u>	Whiting, S.H. and Champoux, J.J., "Properties of Strand Displacement Synthesis by Moloney Murine Leukemia Virus Reverse Transcriptase: Mechanistic Implications," <i>J. Mol. Biol.</i> 278:559-577, Academic Press Limited (May 1998).
	AT	<u>98</u>	Wilson, J.E. et al., "Human Immunodeficiency Virus Type-1 Reverse Transcriptase. Contribution of Met-184 to Binding of Nucleoside 5'-Triphosphate," <i>J. Biol. Chem.</i> 271:13656-13662, The American Society for Biochemistry and Molecular Biology, Inc. (1996).

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AR	<u>99</u>	Wöhrl, B.M. et al., "Footprint Analysis of Replicating Murine Leukemia Virus Reverse Transcriptase," <i>Science</i> 267:96-99, The American Association for the Advancement of Science (1995).
AS	<u>99</u>	Co-Pending U.S. Patent Application No. 09/845,157, Smith et al., filed May 1, 2001.
AT	<u>99</u>	Co-Pending U.S. Patent Application No. 09/808,124, Potter et al., filed March 15, 2001.

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AR	100	Co-Pending U.S. Patent Application No. 09/902,741, Chatterjee, D.K., filed July 12, 2001.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Ninth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Ninth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Eighth Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited and submitted to the Office in Application No. 09/220,329 filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested.

Applicants note that document AT105 ("Clontech's Motion for Partial Summary Judgement of Invalidity (Claim Indefiniteness)") was filed by defendant Clontech together with a memorandum and a motion to file under seal the memorandum. In view of this motion, a copy of the memorandum is not being submitted herewith. The following summarizes Clontech's position as set forth in its memorandum.

Clontech alleges that the claims of U.S. Patent 6,063,608 ("the '608 patent") that recite "as shown in Fig. 5" are *per se* indefinite under 35 U.S.C. § 112, second paragraph, because the '608 patent contains Figs. 5A and 5B, but no Fig. 5.

Clontech alleges that interpreting the term "Fig. 5" to mean Figs. 5A and/or 5B renders the claims invalid, as Fig. 5B purports to be a representation of a gel assay of the wild type enzyme. According to Clontech, since the wild type enzyme is by definition prior art, if the claims cover Fig. 5B, they are anticipated.

Clontech also alleges that Fig. 5A is a composite from at least three sources. Dr. Gerard has testified that he would need to look at the original data in order to confirm whether the gel depicted in Fig. 5A is a composite. Further, Clontech alleges that Counsel

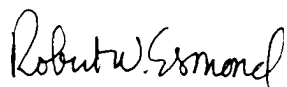
for Invitrogen Corporation (the Patent Owner) has confirmed that the original data has been lost. Clontech contents that these allegations require that the teaching of Fig. 5A is *per se* indefinite.

This Ninth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
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FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942 049000B/RWE/MTT	APPLICATION NO. 10/024,131
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	AR		
	AS	<u>100</u>	"Complaint," dated January 8, 2001, from <i>Invitrogen Corporation v. New England Biolabs, Inc.</i> , U.S. District Court, District of Massachusetts, Civil Action No. 01 CV 10038 WGY
	AT	<u>100</u>	"Complaint," dated February 15, 2001, from <i>Invitrogen Corporation v. Display Systems Biotech, Inc.</i> , U.S. District Court, Southern District of California

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FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>101</u>	"Stratagene's Memorandum in Opposition to Invitrogen's Motion for Preliminary Injunction and Memorandum in Support of Stratagene's Motion for Leave to File an Additional Brief in Opposition to LTI's Motion for Preliminary Injunction...", dated February 27, 2001, with attached Exhibits A-N, from Invitrogen Corporation v. Stratagene Holding Corp., Stratagene, Inc., and Biocrest Manufacturing, L.P., U.S. District Court, District of Delaware, Civil Action No. 00-620 (JJF)
AS	<u>101</u>	"Clontech's Reply in Support of Its Motion for Summary Judgment of Invalidity (Claim Indefiniteness) and in the Alternative for a Claim Construction, and Clontech's Opposition to Invitrogen's Cross-Motion for Summary Judgement," dated March 14, 2001, with attached Exhibits I and J, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
AT	<u>101</u>	"Order" and attached "Memorandum Opinion," dated May 4, 2001, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449 <u>NINTH SUPPLEMENTAL</u> <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 0942.049000B/EWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>102</u>	"Clontech's Notice Pursuant to 35 U.S.C. § 282," dated May 10, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
AS	<u>102</u>	"Order" and attached "Memorandum Opinion," dated May 22, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
AT	<u>102</u>	"Clontech's Supplemental Pretrial Order," dated May 25, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action No. AW 00-1879 (consolidated w/AW 96-4080)

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.



FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>103</u>	"Order" dated May 25, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AS	<u>103</u>	"Responsive Expert Statement of Joseph O. Falkinham, III," dated May 31, 2001, from <i>Clontech Laboratories, Inc. v. Life Technologies, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action No. AW 00-1879
	AT	<u>103</u>	"Order" and attached "Memorandum Opinion," dated July 6, 2001, from <i>Invitrogen Corporation v. Stratagene Holding Corp. et al.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action No. AW 01-1168

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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## FOREIGN PATENT DOCUMENTS

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	104	"Report and Recommendation Regarding Clarification of the Court's Orders Dated May 4, 2001 and May 24, 2001," dated August 8, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AS	104	"Defendant Clontech Laboratories, Inc.'s Objections to the Special Master's Report and Recommendation Regarding Clarification of the Court's Orders Dated May 4, 2001 and May 24, 2001," dated August 17, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AT	104	"Invitrogen Corporation's Objections to the Special Master's Report and Recommendation Regarding Clarification of the Court's Orders Dated May 4, 2001 and May 24, 2001," dated August 22, 2001, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879

EXAMINER	DATE CONSIDERED
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FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>105</u>	"Defendant Clontech Laboratories, Inc.'s Response to Plaintiff Invitrogen Corporation's Objections to the Special Master's Report and Recommendation Regarding Clarification of the Court's Orders Dated May 4, 2001 and May 24, 2001," dated August 31, 2001, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AS	<u>105</u>	"Complaint for Patent Infringement and Inducement to Infringe," dated September 6, 2001, from Invitrogen Corporation v. Toyobo Co., Ltd., U.S. District Court, Southern District of California, Civil Action No. 01 CV 1628 W (JFS)
	AT	<u>105</u>	"Clontech's Motion for Partial Summary Judgment of Invalidity (Claim Indefiniteness)," dated September 27, 2001, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>106</u>	"Brief of Defendants-Appellees," dated October 5, 2001, from Invitrogen Corporation v. Stratagene Holding Corp., Stratagene, Inc., and Biocrest Manufacturing, L.P., U.S. Court of Appeals for the Federal Circuit, Civil Action No. AW-01-1168
	AS	<u>106</u>	"Order," dated October 5, 2001, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AT	<u>106</u>	"Complaint," dated October 17, 2001, from Invitrogen Corporation v. Incyte Genomics, Inc., U.S. District Court, District of Delaware, Civil Action No. 01-692

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449 NINTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>107</u>	"Rebuttal Expert Statement of Joseph O. Falkinham, III," from <i>Clontech Laboratories, Inc. v. Life Technologies, Inc.</i> , U.S. District Court, District of Delaware, Civil Action No. 98-750 (SLR)
AS	<u>107</u>	"Expert Statement of Joseph O. Falkinham, III," with attached Exhibits 1-3, from <i>Clontech Laboratories, Inc. v. Life Technologies, Inc.</i> , U.S. District Court, District of Delaware, Civil Action No. 98-750 (SLR)
AT		

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Tenth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Applicants wish to bring the following information to the attention of the U.S. Patent and Trademark Office. Defendant Clontech has filed in U.S. District Court, District of Maryland, Southern Division (Civil Action Nos. AW 96-4080 and AW 00-1879) two confidential declarations by its expert Joseph O. Falkinham, III subject to a protective order ("Attorneys Eyes Only"). In view of the protective order, copies of the declarations are not being submitted herewith. The following summarizes defenses set out in the declarations.

The declarations allege that the following terms and phrases recited in the claims of parent U.S. Patent Nos. 5,244,797, 5,668,005 and 6,063,608 are indefinite and render the claims invalid: "without significant degradation," "the RNA template," "organism is a retrovirus," "said organism" and "derived from." In particular, the declarations allege that a retrovirus is not an organism. The declarations also allege that it is not clear whether "derived from" means "directly isolated" or whether further manipulation is required. In addition, one declaration alleges that the following phrases recited in the claims of U.S. Patent No. 6,063,608 are indefinite and render the claims invalid: "reduction of RNase H

activity is determined by examining the integrity of an mRNA template during cDNA synthesis" and "modifying a nucleotide sequence."

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

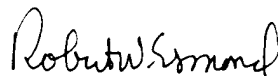
This Tenth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of this Tenth Supplemental Information Disclosure Statement and making the same of record in the prosecution of the above-identified application is respectfully requested.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Eleventh Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Eleventh Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Tenth Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited by and submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.



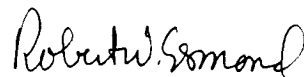
Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

This Eleventh Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449 ELEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

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	AA						
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR		
	AS		
	AT	<u>107</u>	"Answer," dated November 21, 2001, from Invitrogen Corporation v. Incyte Genomics, Inc., U.S. District Court, District of Delaware, Civil Action No. 01-692

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  ELEVENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	108	"Reply Memorandum in Support of Clontech's Motion for Partial Summary Judgement of Invalidity (Claim Indefiniteness) and Opposition to LTI's Motion for Partial Summary Judgment of Definiteness," dated November 1, 2001, with attached Exhibits 1-3, from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court, District of Maryland Southern Division, Civil Action No. AW 96-4080 and AW 00-1879.
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	AT		

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Twelfth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 is a document that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Twelfth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Eleventh Supplemental Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited and submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

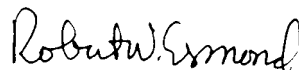
Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

This Twelfth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449  TWELFTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

## U.S. PATENT DOCUMENTS

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR		
	AS	108	"Clontech's Memorandum in Support of Its Motion for Partial Summary Judgment That the Claims of the Patents-in-suit are Invalid for Failing to Satisfy the Written Description Requirement of 35 U.S.C. § 112, First Paragraph," dated December 28, 2001, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court, District of Maryland, Southern Division, Civil Action Nos. AW 96-4080 and AW 00-1879
	AT		

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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Thirteenth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Thirteenth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Twelfth Information Disclosure Statement filed herewith in connection with the above-captioned application. All documents were cited and submitted to the Office in Application No. 09/220,329, filed December 24, 1998.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

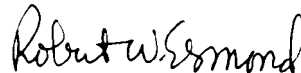
Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

This Thirteenth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003  
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Washington, D.C. 20005-3934  
(202) 371-2600-ODMA MHODMA SKGE\_DC1:96647.1





FORM PTO-1449

THIRTEENTH SUPPLEMENTAL  
INFORMATION DISCLOSURE STATEMENTATTY. DOCKET NO.  
0942.049000B/RWE/MTTAPPLICATION NO.  
10/024,131APPLICANTS  
Kotewicz et al.FILING DATE  
December 21, 2001GROUP  
1652

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
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## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>109</u>	Krug, M.S., and Berger, S.L., "[33] First-Strand cDNA Synthesis Primed with Oligo(dT)," <i>Meth. Enzymol.</i> 152:316-325, Academic Press, Inc. (September 1987)
	AS	<u>109</u>	Mölling, K., et al., "Association of Viral Reverse Transcriptase with an Enzyme degrading the RNA Moiety of RNA-DNA Hybrids," <i>Nature New Biology</i> 234:240-243, Macmillan Journals Ltd. (1971)
	AT	<u>109</u>	"Memorandum in Support of Clontech's Motion for a Summary Judgment of Invalidity (Claim Indefiniteness), or in the Alternative, Motion for a Claim Construction," dated February 14, 2001, with attached exhibits A-H from <i>Invitrogen Corporation v. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080 and AW-00-1879

EXAMINER

DATE CONSIDERED

**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449  THIRTEENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.0490001B RWE MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

AR	<u>110</u>	"Report and Recommendation Regarding (1) Invitrogen Corporation's Motion for Partial Summary Judgement That the Work of Goff et al Is Not Prior Art to the Patents-In-Suit, (2) Clontech's Cross Motion for Summary Judgement That the Work of Goff et al Is Invalidation [sic] Prior Art Under 35 U.S.C. § 102(g) or In Alternative Is Admissible Evidence at Trial, and (3) Clontech's Motion In Limine to Exclude Evidence of the Work of Goff et al at Trial for Prior Art," dated January 15, 2002, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080 and AW-00-1879
AS	<u>110</u>	Letter to Philip G. Hampton, II, from Robert J. Koch, dated January 31, 2002, regarding Invitrogen Corporation v. Clontech Laboratories, Inc., Civil Action No. AW-96-4080 and AW-00-1879
AT	<u>110</u>	Letter to Philip G. Hampton, II, from Marc R. Labgold, dated February 1, 2002, regarding Invitrogen Corporation v. Clontech Laboratories, Inc., Civil Action No. AW-96-4080 and AW-00-1879

EXAMINER

DATE CONSIDERED

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	APPLICANTS Kotewicz et al.	
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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>111</u>	Invitrogen Corporation v. Stratagene Holding Corporation, Stratagene, Inc., and Biocrest Manufacturing, L.P., 2002 U.S. App. Lexis 3613 (Fed. Cir. 2002)
	AS	<u>111</u>	Letter to Robert J. Koch from Philip G. Hampton, II, dated February 21, 2002, regarding Invitrogen Corporation v. Clontech Laboratories, Inc., Civil Action No. AW-96-4080 and AW-00-1879
	AT	<u>111</u>	"Clontech's Reply Memorandum in Support of Its Motion for Partial Summary Judgment of Invalidity (Written Description) and Opposition to LTI's Motion for Partial Summary Judgment," dated March 4, 2002, from Invitrogen Corporation v. Clontech Laboratories, Inc., U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080 and AW-00-1879

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THIRTEENTH SUPPLEMENTAL  
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	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>112</u>	"Order," dated March 18, 2002, from <i>Invitrogen vs. Clontech Laboratories, Inc.</i> , U.S. District Court for the District of Maryland, Southern Division, Civil Action No. AW-96-4080 and AW-00-1879
	AS	<u>112</u>	
	AT	<u>112</u>	

EXAMINER

DATE CONSIDERED

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kotewicz *et al.*

Appl. No. 10/024,131

Filed: December 21, 2001

For: **Cloned Genes Encoding Reverse  
Transcriptase Lacking RNase H  
Activity**

Confirmation No. 4058

Art Unit: 1652

Examiner: *To Be Assigned*

Atty. Docket: 0942.049000B/RWE/MTT

**Fourteenth Supplemental Information Disclosure Statement**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Applicants wish to bring the following information to the attention of the U.S. Patent and Trademark Office. Applicants' undersigned representative recently became aware that ClonTech filed excerpts of an "Expert Statement of Joseph O. Falkinham, III," ClonTech's technical expert, attached to its "Reply in Support of its Motion for Summary Judgment of Invalidity (Non-Enablement)." Because these documents are subject to a protective order ("Attorney's Eyes Only"), copies cannot be provided to the Examiner without violating a court order. Therefore, copies are not being provided for consideration by the Examiner. However, in order to complete the record as to what was contested before the District Court on the issue of enablement, Applicants provide the following information regarding Falkinham's Statement.

In contrast to Dr. Champoux's affidavit, the excerpts from Falkinham's Statement presents the following arguments:

That Applicants' specification states that the active site of the MMLV RT RNase H was not known at the time the application was first filed and, as a result, one would have to introduce point

mutations throughout approximately 2000 nucleotides in order to obtain RNase H-deficient point mutants.

That, despite extensive experimentation over years, LTI was unable to make an RNase H-deficient mutant using smaller deletions or point mutations until the publication of Repaske *et al.* (reference AR18) and Kanaya *et al.* (reference AS17) which taught exactly what mutations should be made that affected the RNase H activity.<sup>1</sup>

That, while Johnson *et al.* (reference AT5) disclose conserved sequences in proteins encoded in retroviral pol genes and the *E. coli* RNase H gene, those conserved sequences are not identified as having any role in RNase H catalytic activity. In order to use the data in Johnson *et al.* to guide the choice of oligonucleotides for site-directed mutagenesis to substantially reduce RNase H activity, one would have to know what amino acids are involved in catalytic activity. That information was not provided by Johnson *et al.* or other publications at the time of filing.

That one who was aware of Johnson *et al.* would not have known where to direct site-directed mutagenesis in the region encoding the RNase H activity. Even if one were to focus only on the conserved sequences in this region, there are 5 sequences, including approximately 17 amino acids (51 nucleotides) that one could have considered changing. The LTI notebooks indicate that one single amino acid change did not produce the desired result and three mutations were required. To determine which 3 nucleotide changes should be made would require testing 132,651 combinations. Thus, Johnson *et al.* would have not enabled one to make an RNase H-deficient point mutant.

That the testimony of inventor Kotewicz indicates that the inventors had not enabled one to prepare point mutants.

That the specification does not enable one to obtain RNase H deficient mutant RTs from any virus other than MMLV. Hizi *et al.* (reference AT16) demonstrate that deletion mutations did not result in a mutant of the HIV-RT that meets the limitations of the patent

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<sup>1</sup>However, as pointed out in "Invitrogen Corporation's Summary Judgment Reply Brief on Enablement issues," also subject to a protective order ("Attorneys Eyes Only"), Clontech presented no evidence that Invitrogen ever attempted to prepare a point mutant until Brian Schmidt's successful preparation of one in 1990. There was a 1989 report that makes reference to a mutant that was designed to change the amino acid sequence of RT, referring to a point mutant. This document states that the mutant was to be generated in January [1990].

claims.<sup>2</sup> This is because, in part, HIV-RT is a dimer, a feature not contemplated by the inventors.

That LTI had difficulty in creating an RNase H-deficient RT mutant from a source other than MMLV. LTI spent years trying to obtain an RNase H-deficient mutant from RSV and AMV, and LTI had not succeeded in bringing such a product to market.<sup>3</sup>

That there is no teaching of an enzyme in the specification that has "substantially no RNase H activity" as defined in the specification.

That the specification does not demonstrate any mutant RT capable of improving cDNA yield, length, or any other improvement over the prior art in the generation of full length cDNA. The proposed utility of more cDNA being produced could have been the result of a mutant polymerase better able to displace viral RNA and not because of an RNase H mutation. This was not contemplated by the specification.

That his opinion is consistent with the reviewer's comments (references AR20 and AS20) who criticized the inventors' manuscript that served as a basis for drafting the specification. The reviewer had commented that 34% versus 24% yield was not a significant difference.

That in response to the reviewer's comments, the manuscript was revised to state that the enzymes were of equal efficiency. Thus, the inventors acknowledged in their published paper (reference AT6) that the enzymes in the patent did not meet the claim limitations and were not improved over the prior art.

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure

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<sup>2</sup>However, as pointed out in "Invitrogen Corporation's Summary Judgment Reply Brief on Enablement issues," Hizi *et al.* describe a "carboxy-terminal deletion mutant, CT-16, that retains significant levels of polymerase activity but has no detectable RNase H activity" in HIV-RT. Hizi *et al.* at 577.

<sup>3</sup>Invitrogen's U.S. Appln. No. 09/064,057, filed April 22, 1998 (see document AT113), describes the preparation of RNase H deficient mutants from RSV and AMV RTs.



requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Fourteenth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Thirteenth Information Disclosure Statement filed on herewith in connection with the above-captioned application. A copy of each document is also provided.

The Examiner's attention is directed to co-pending U.S. Patent Application Nos.:

U.S. Patent Application No. 09/064,057, filed April 22, 1998, U.S. Patent Application No. 09/245,025, filed February 5, 1999, U.S. Patent Application No. 10/292,604, filed November 13, 2002 and U.S. Patent Application No. 10/292,662, filed November 13, 2002. The specifications of US patent application Nos. 09/064,057, 09/245,025, 10/292,604 and 10/292,662 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AT113**.

U.S. Patent Application No. 09/076,115, filed May 12, 1998, submitted herewith as document **AR114**;

U.S. Patent Application No. 09/220,329, filed December 24, 1998, U.S. Patent Application No. 09/220,330, filed December 24, 1998 and U.S. Patent Application No. 10/024,149, filed December 21, 2001. The specifications of US patent application Nos. 09/220,329, 09/220,330 and 10/024,149 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AS114**.

U.S. Patent Application No. 09/266,935, filed March 12, 1999, submitted herewith as document **AT114**;

U.S. Patent Application No. 09/533,548, filed March 23, 2000, submitted herewith as document **AR115**;

U.S. Patent Application No. 09/570,526, filed May 12, 2000, submitted herewith as document **AS115**;

U.S. Patent Application No. 09/603,613, filed June 26, 2000, and U.S. Patent Application No. 10/337,421, filed January 7, 2003. The specifications of US patent application Nos. 09/603,613 and 10/337,421 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AT115**.

U.S. Patent Application No. 09/608,066, filed June 30, 2000, submitted herewith as document **AR116**;

U.S. Patent Application No. 09/697,079, filed October 27, 2000, submitted herewith as document **AS116**; and

U.S. Patent Application No. 10/224,334, filed August 21, 2002, submitted herewith as document **AT116** are directed to related technical subject matter.

The identification of these U.S. patent applications is not to be construed as a waiver of secrecy as to these applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on

information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

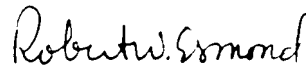
This Fourteenth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and

Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert W. Esmond  
Attorney for Applicants  
Registration No. 32,893

Date: March 5, 2003

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Washington, D.C. 20005-3934  
(202) 371-2600

FORM PTO-1449  FOURTEENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. C942.049000B/RWE/MTT	APPLICATION NO. 10/024,131
	APPLICANTS Kotewicz et al.	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH1	6,140,086	10/31/2000	Fox et al.			08/14/1998
	AI1	2002/0028447 A1	03/07/2002	Li et al.			02/29/2000
	AJ1	6,399,334 B1	06/04/2002	Li et al.			09/23/1998
	AK1	6,518,019	02/11/2003	Gerard et al.			02/05/1999

FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL						Yes No
	AM1	WO 98/47912 A1	10/29/1998	WIPO			Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR		
	AS	112	Hizi, A. et al., "Effects of Small Insertions on the RNA-Dependent DNA Polymerase Activity of HIV-1 Reverse Transcriptase," Virol. 170:326-329, Academic Press, Inc. (1989).
	AT	112	Hizi, A. et al., "Mutational Analysis of the DNA Polymerase and Ribonuclease H Activities of Human Immunodeficiency Virus Type 2 Reverse Transcriptase Expressed in <i>Escherichia coli</i> ," Virol. 180:339-346, Academic Press, Inc. (1991).

EXAMINER	DATE CONSIDERED
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U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA2	2002/0177155 A1	11/28/2002	Li et al.			05/13/2002
	AB2	6,495,350 B1	12/17/2002	Lee et al.			12/23/1999
	AC						
	AD						
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
AR	<u>113</u>	Hostomsky, Z., et al., "Reconstitution in vitro of RNase H activity by using purified N-terminal and C-terminal domains of human immunodeficiency virus type 1 reverse transcriptase," <i>Proc. Natl. Acad. Sci. USA</i> 88:1148-1152, National Academy of Sciences (1991).	
AS	<u>113</u>	Declaration of James J. Champoux with Exhibits 1-11 attached, filed December 16, 2002 in parent U.S. Patent Application No. 09/220,329.	
AT	<u>113</u>	Pending United States Patent Application Nos. 09/064,057, 09/245,025, 10/292,604 and 10/292,662, Gerard et al., filed April 22, 1998, February 5, 1999, November 13, 2002 and November 13, 2002 respectively.	

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AR	<u>114</u>	Pending United States Patent Application No. 09/076,115, Gruber et al., filed May 12, 1998.	
AS	<u>114</u>	Pending United States Patent Application Nos. 09/220,329, 09/220,330 and 10/024,149, Kotewicz et al., filed December 24, 1998, December 24, 1998 and December 21, 2001 respectively.	
AT	<u>114</u>	Pending United States Patent Application No. 09/266,935, Li et al., filed March 12, 1999.	

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	AR	<u>115</u>	Pending United States Patent Application No. 09/533,548, Hughes, A. John R., filed March 23, 2000.
	AS	<u>115</u>	Pending United States Patent Application No. 09/570,526, Astatke et al., filed May 12, 2000.
	AT	<u>115</u>	Pending United States Patent Application Nos. 09/603,613 and 10/337,421, Lin et al., filed June 26, 2000 and January 7, 2003 respectively.

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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>116</u>	Pending United States Patent Application No. 09/608,066, Astatke et al., filed June 30, 2000.
	AS	<u>116</u>	Pending United States Patent Application No. 09/697,079, Fox et al., filed October 27, 2000.
	AT	<u>116</u>	Pending United States Patent Application No. 10/224,334, Lee et al., filed August 21, 2002.

EXAMINER	DATE CONSIDERED
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**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.